Transcript

Fourth Meeting of the Secretary's Advisory Committee on Xenotransplantation, U.S. Department of Health and Human Services

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Plenary Sessions

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Reported By:

L.A.D. Reporting Company
1684 East Gude Drive, Suite 201
Rockville, Maryland 20850
(301) 762-8282

P R O C E E D I N G S 8:30 A.M.

Agenda Item: Xenotransplantation: Meeting Updates, News Items, Activity Updates

DR. VANDERPOOL: Let's take our seats and proceed with the second day of DHHS Secretary's Committee on Xenotransplantation. We do have a busy morning of activities. Some of the things on the schedule that our SACX committee members and our nonvoting members have received will be adjusted somewhat as we go along. We'll be clear about those changes. Before we move to our first item on this list of meeting updates, news items and activity updates, I just want to recognize some of the staff who make these meetings possible. I want you to know that Paul and all of the people who are helping this meeting occur are greatly appreciated. It includes Mannie Harris, the person in charge of all the recording and so on, and our two court reporters, Sharon Livingston and Tammy Jaffe. As the Chair I think I speak on behalf of committee members that we greatly appreciate the conveniences that you have provided for us.

The first item on the agenda today is a brief overview of the February 2002 meeting of the European Agency for evaluation of medicinal products. And we're again fortunate to have Dr. Eda Bloom make that brief presentation to us. Eda?

Agenda Item: Brief overview of the February 2002 meeting of the European Agency for Evaluation of Medicinal Products

DR. BLOOM: Good morning. On February 5th the European Agency for the Evaluation of Medicinal Products, which is for some reason abbreviated EMEA, held a meeting because they are planning to issue a points to consider, which is a guidance document, about xenogeneic cell therapies. Dr. Chapman was also in attendance at that meeting. We were two representatives from the U.S. There were representatives that had been invited to talk about safety issues, including animal husbandry, porcine endogenous retrovirus, other microbiological potential problems, other efficacy problems. And the following day the committee was going to begin to draft a guidance. The committee that's charged with this is called the Committee for Proprietary Medicinal Products, which is one of three committees that the EMEA uses, the other two dealing with orphan and with veterinary products. This particular committee has several working parties, which I won't trouble you with the names of those, but the important part is that usually EMEA drafts points to consider when a product is in widespread use so that there is experience that they can use to draw on. In the case of xenogeneic cells they felt that they wanted to draw on other international experience in order to draft a guidance before it was being used. This guidance will be issued on behalf of the European Union. It will also take into consideration a list of recommendations that is in the process of being finished by the Council of Europe, which is another arm of the European Environment, and I'm afraid I'm not an expert on the role of the Council of Europe versus the European Union and then the roles of the individual member states, individual agencies, but in many cases they're all doing something having to do with xenotransplantation to try to ensure its safety.

DR. VANDERPOOL: Any questions or comments to Dr. Bloom about her remarks? The second item is an announcement of the PERV immunoassay workshop. Dr. Carolyn Wilson we have learned is a very valued researcher in the field from the FDA CBER, and so we thank her for being here and for making this announcement to us. Thank you, Dr. Wilson.

Agenda Item: Announcement of PERV Immunoassay Workshop

DR. WILSON: Thank you. I just wanted to actually make a very brief announcement to make members of the SACX committee aware, as well as members of the public, that we are going to have a workshop to

discuss the state of PERV immunoassays tentatively scheduled for October 10th, 2002. It will be held at the NIH campus in Wilson Hall, which is located in building 1. This workshop is in direct response to committee discussion and recommendations that were made at the November 2001 meeting. As you may recall, I presented there the results of sponsors' experience with detection of evidence of infection for porcine endogenous retrovirus in subjects that are in xenotransplantation clinical trials, and the committee expressed concerns about the state of the assays that were used for detection of PERV-specific antibodies. In particular there was concern because in some subjects there would be an antibody response in the pretreatment samples. This obviously makes the utility then of an immunoassay for screening for evidence of infection to be suspect because you can't interpret the data at post-treatment time points. So as an outcome of that discussion, members of the committee had recommended that if we developed a central repository of the reagents that were used in those types of immunoassays, that would allow for cross-lab comparison ultimately leading to refinements in the assays that were used.

So this workshop then is going to bring together members of government agencies, private industry, as well as academic laboratories, who are working in this area of developing reagents for PERV immunoassays. Specifically what we hope to get out of this workshop is to determine first what reagents are available for these assays, what assays are available, and what type of data is available from these assays, leading to development of a public repository of reagents that would facilitate exchange between laboratories and improve existing assays. It's hoped that development of better assays would lead to improved data allowing for better evaluation of the safety of porcine xenotransplantation clinical trials. And I hope that the committee will be able to participate in this workshop in October. Thank you for your attention.

DR. VANDERPOOL: Thank you, Dr. Wilson. Are any members of the committee planning to attend that workshop? Great. Tony? That's terrific. Thanks so much. We're glad the workshop will be occurring in a timely way. Also I would appreciate it, Dr. Wilson, if you could just put that information on a sheet and have Dr. Groesch -- Okay. We have your slide. Great. Thanks.

Third on the agenda is information and recommendations for physicians involved in the co-culture of human embryos with nonhuman animal cells. And again we turn to Dr. Eda Bloom for that report.

Agenda Item: Information and Recommendations for Physicians Involved in the Co-Culture of Human Embryos with Nonhuman Animal Cells

DR. BLOOM: I guess I don't have to say good morning again, huh. On last Friday FDA issued a letter to assisted reproductive technology centers that we had identified as performing a procedure which involves the culture of fertilized egg on monolayers of nonhuman cells. Now, as you probably know from the many times you've heard the definition of xenotransplantation, this procedure falls within the umbrella of the second part of the definition, that is, implantation into a human recipient of human cells that have been exposed ex vivo to nonhuman cells. It is a procedure that has been going on for ten years or so, and because of the amount of time that this procedure has been going on, FDA decided to act with deliberation and sensitivity in issuing this letter. The letter can be found on the Internet at any number of CBER sites, and I can give those to you if you're interested, but if you just go to CBER at What's New, that's one way of finding it.

DR. GROESCH: Eda, I'll just point out that it's in your briefing notebooks too, a copy of that.

DR. BLOOM: Thank you. The bottom line is that any procedure of this type that is performed from now on will require an IND with the Food and Drug Administration. Those procedures that have occurred until now, our request is that the physicians that have performed these procedures and perhaps the women who have undergone these procedures call us to learn of any safety precautions that we would

recommend. That's it.

DR. VANDERPOOL: Questions or comments for Dr. Bloom? Bill?

DR. SCHECKLER: I had sort of agreed at the last meeting to track down Jamie Thompson at the University of Wisconsin and find out a little bit more myself. I couldn't get to Jamie, but I got to a colleague in the medical school where they use hematopoietic stem cells, which are used just to cell separate at infusion. They are never grown out. But embryo derived human stem cells are grown on a mouse fibroblast lawn which has growth promoting factors most of the human cell lines don't have, plus a complex media that's full of various kinds of promoters, enzymes and so forth, and they're working diligently to find a human cell lawn that will work. So what I'm assuming is that you're saying in the embryo research or in the fertility clinic they're using the same type of mouse cell lawn, and I guess what I'd like to know and what I don't know -- and I haven't been able to visit the lawn myself to see how it's mowed -- is what do we know about any kind of viruses or anything else in that lawn? Because as I understand it, these cells have been used for a very long time.

DR. BLOOM: Actually the types of cells that are being used in fertility clinics are not the mouse cell lines that you're speaking of. The ones that we have identified include the use of vero cells, which is an African green monkey kidney cell line. It is also a long established line. We'll have to look very carefully at that one. Other cell types include -- these have all been published by the way. There's a cell line of bovine origin, and it appears that what also has been used are fresh bovine cells, which of course would be of more concern to us. There is also a cell line from a particular rat strain that has been used. So there's a lot of creativity. And the purpose of the ex vivo culture for fertilization for fertility treatment is different than that for embryonic stem cells. The idea is to enable the zygote to grow into a blastocyst or close to it before implantation, the idea being that that would help the implantation process, that that would be an effective way of increasing implantation frequency. Again what we know is primarily from the literature, and the literature is a little bit ambivalent on this point. I have seen some reports, notably from French laboratories where this has gone on for a longer period of time with more patients, that there is some basis to this, but not all the published reports say that, and I'm not aware of any good study that has been done to show that this is really a beneficial procedure or not.

DR. VANDERPOOL: Dr. Salomon?

DR. SALOMON: Eda, I haven't obviously had a chance to read the whole letter, so it might be in here, but my thinking would be that if there were one, maybe two lines that were particularly efficacious for this purpose, that there could be a very specific effort mounted to demonstrate, at least within current technology, that these were not possessing a productive infection of viral or other origin and that then couldn't you not do this under IND then after that?

DR. BLOOM: Yes and yes. Of course, as you know with Epicel, the subcommittee talked about what kinds of studies should be done to ensure that the cell line was safe within the scope that we can understand, and of course the same kind of thing could be done here, and that's what we would ask for under an IND. It's very straightforward actually.

DR. ALLAN: There was a recent publication growing these cells not on fetal layers and that there was some success with that as well I think.

DR. BLOOM: I think you're probably talking about embryonic stem cells, which is a different issue. And you're right. There was a publication that they've been able to wean them off.

DR. VANDERPOOL: Dan?

DR. SALOMON: I just had to go off in a second direction, and that is I guess one response I had when you were going through that saying you were then going on to specifically ask physicians in this area to notify mothers, for example, or families really, since it's not just the mother affected by this, that they had had in vitro fertilization or were in contact with these and that there were unknowns now. I guess that kind of bothers me a little bit in the sense that is that responsible to lay all that on these poor people when it's not like there's a smoking gun here?

DR. BLOOM: No, there's misunderstanding. We're not asking the physicians to notify the mothers. We're asking physicians to call us so that when they now go ahead and do more procedures, they can discuss. We're not asking them to notify previous ones, but we are putting a public blurb on our website that if a woman who has had this procedure happens to for whatever reason happen upon this site, we're asking that they call us directly.

DR. SYKES: Do you have any idea how widespread this procedure is in the U.S., and who are you going to send the letter to?

DR. BLOOM: The letter has been sent to about 12 fertility clinics that have been definitively identified as publishing on this procedure. We're having investigators that have published on the procedure. We estimate that in total there may be as many as 30 or so clinics that are doing or have done this. We also know that there are clinics that have done it that have stopped doing it, so it's not really clear at this point.

DR. VANDERPOOL: Prior to our meeting in November, Dr. Groesch called, and we talked about this issue, and there's been some discussion between the agencies. I understand, Dr. Groesch, that this committee might need to deal with the xeno dimensions of stem cell research and so on. Is that correct? If that's the case, then maybe as we look forward at the very end of this meeting about future agenda items, we would want to discuss this in greater detail and perhaps have a more formal report about it in terms of the information base and so on so we could certainly be able to say, well, as the advisory committee on xenotransplantation, we're aware of this issue, we've talked about it, and our views are as follows. Any comment from you on both the negotiations on the one hand, Mary, and perhaps this is an agenda item in the future on the other?

DR. GROESCH: Well, I think that the stem cell issue isn't such a current one for the xenotransplantation committee, and there are in fact other advisory groups within the department that have been established to deal specifically with stem cell issues. Dr. Patterson? Oh, okay. So I think that for right now, and in fact, it came up with the science working group that they don't think that that's a very current issue right now, that it's down the line maybe several years and that there's more pressing issues for this group to deal with, more specifically, the xenotransplantation.

DR. VANDERPOOL: So this is something to keep our eye on because if it does become an important issue, it's one thing to talk about which stem cell lines are legitimate and so on, it's quite another to talk about the very specific aspects of xeno that may be involved. And this committee is supposed to be the one and is fast becoming the one to be able to think through some of those issues if indeed they become prominent in that area. Dr. Patterson?

DR. PATTERSON: I'll reserve my comment till public comment.

DR. VANDERPOOL: At public comment. Great. Okay. Professor Shapiro?

MS. SHAPIRO: I just had a question for Mary. Is the sense that it's not urgent because the stem cell lines that have been approved for federal funding probably aren't going to be used in clinical trials?

DR. GROESCH: Dan, I think you can speak more about the discussion that the science working group had on this.

DR. SALOMON: Yeah. I think that the issue is it's not going to happen to clinical trials any time in what we at least foresee.

MS. SHAPIRO: In the publicly funded sector, but in the private sector are you sure?

DR. SALOMON: I'd be an idiot to say I'm sure, but I don't think that at this point what they'd be doing in the private sector, if they were really rushing forward to do some sort of a clinical trial, which they can't do without an IND, so that would trigger us anyway. Now, what they might do in Mexico or the Cook Islands or something is another discussion and a scary one, but for right now I just don't think that this is where we want to go.

DR. VANDERPOOL: One reminder though, and that is this is the xenotransplantation committee, and we need not confine our attention to clinical trials insofar as those issues do come up in other arenas. And if Dan just gave the proviso that he's the last one to guess, I will triple the odds that I'm the last one to guess what should happen on these issues, but to stay open for it. And I think we are. And thank you, Dr. Bloom, for your report.

One other agenda item that I mentioned in my opening remarks yesterday is that we have had a change in our charter, and I wanted to bring that to the attention of the committee for any comment if there is such. This is under tab 2 of our notebooks. If you'll recall, some significant concern was addressed particularly by the FDA that the word review in the second item of our charter, review current and proposed xenotransplantation clinical trials, connoted a level of activity that would approach IRB and FDA review of clinical trials. So in lieu of deleting that entire phrase, the committee voted unanimously that it be changed, and you'll see the change offered on this page about the change. Now, a line is drawn through the first two sentences. Actually that doesn't mean at all that those sentences were deleted. Rather, the only change in the sentence is instead of review current and proposed xenotransplantation clinical trials, be informed about current and proposed xenotransplantation clinical trials. So that's the only change. This is something that Mary Groesch called myself and probably some others of you about. It seems to be an appropriate change. Be informed seems to me is in keeping with the spirit of the recommendations of our committee at our last meeting. Are there any comments about that change? So I assume that everyone is in agreement with that change in our charter.

DR. SALOMON: Just as a point of clarification, Harold, who will review these?

DR. VANDERPOOL: The trials are being thoroughly reviewed in an IRB fashion in terms of particular harms and benefits and so on by the FDA at this time that has that power and purview to review in this very specific sense. I think the desire of the FDA is that we're not a group that looks over their shoulder in terms of their particular scientific review. Does that answer what your question is?

DR. SALOMON: (Whereupon, nods head in the affirmative.)

DR. VANDERPOOL: I mean I don't think that by being informed, we'll know what's going on with respect to what the trials are, and we can make requests to that degree and what's happening and how many trials are being done and so on, as we received in our formal reports, but having been on an IRB and still actively on an IRB, I wouldn't relish the thought that this committee would in nonpublic closed meetings become a substitute IRB. That was the concern of the FDA.

DR. ALLAN: The only question I would have is what would be the process of being informed? In other words, would it be like a year after the clinical trial has gone on? I mean the issue is that the information is pipeline maybe.

DR. VANDERPOOL: Jon, the phrase be informed is one of those wonderful phrases that can go all the way. It depends on your modifiers. Become thoroughly informed? Become informed well after the fact? No. Be informed. And I'm sure Dr. Bloom has more than one sentence to say about this. Dr. Bloom?

DR. BLOOM: I think what we have done with other advisory committees in this arena is we've given annual updates. If there is an IND that comes in that needs further discussion in our estimation, that will trigger a more extensive discussion here. If for example we were to get an organ transplant out of the blue, I mean that clearly would be here. If we were to get another IND where we have ex vivo culture on 3T3 cells, it would not, and I don't think you need to know about that when it happens. I don't think you want to. And so I'm afraid that you're going to have to trust our judgment in that regard, but I think it's a valid judgment. You may or may not have noticed, for example, in the web posting of the material that is going out that is up about the ex vivo culture of zygotes at the blastocyst stage, we recommend further public discussion of that. So if there were to be an IND to come in, and hopefully even before there's an IND to come in, we can get discussion on that one.

DR. ALLAN: I don't want to get into a long discussion on this, but there's two things that came to mind for me. One was there was a -- and I don't want to put you on the spot here, but you put out for public comment on making both xenotransplantation and gene therapy trials at least some information open to the public, and there was a period for response to that, and I was sort of curious as to what was happening with that.

DR. BLOOM: We received lots and lots and lots of public comment, not all of it saying how wonderful we are, and we are in the process of trying to revise the document. It's going to be a substantial revision. It will likely be again in draft form rather than a final rule, but all I can say is we're working on it.

DR. VANDERPOOL: Is it fair to say that the sense of the committee is that the phrase be informed means something like continuing updates on major developments and new trial initiatives?

MR. BERGER: I'd just like to follow up on the comment that Jon made. I had just asked Eda about that too beforehand. I am concerned that the comment period's been over for almost a full year, and I am concerned that this might just sit there and not go forward. This committee has had a lot of discussions about bringing the public more involved in the entire xenotransplantation issue, and I'd like to see the committee make a recommendation that that proposed rule be adopted.

DR. VANDERPOOL: Can we put that on the agenda for discussion at the next meeting? Okay. And is it the sense of the committee that continuing updates is the way we're looking at this in terms of new developments and new initiatives? Okay. As well as ongoing protocols.

Now let's move to the question that we need to handle briefly, and that is the suggestion from Dr. Dan Salomon yesterday about whether this committee should make a comment recommendation and bring it to the attention of the Secretary of the New Zealand trials that are being conducted in Mexico. Now, I'm going to make sure our time here is limited because we do have other items on the agenda, but quickly what are some of the SACX committee and the nonvoting committee member comments about this proposal? In my own judgment we need to think seriously about whether this committee right out of the chute, the first recommendation to the Secretary deals with an issue of two national entities, one from New Zealand doing work in Mexico. On the other hand, there are safety concerns I think we have. So bring this to the attention of the Secretary? Probably yes. Make a recommendation about it? I'm worried

about that kind of language. So let's talk about it. Dr. Sykes? And when someone finishes, hold up your hand, put your light on and proceed.

DR. SYKES: Well, I think that there is some urgency to bringing this to the attention of the Secretary, and I think it would be a mistake to wait until we have our ultimate report before bringing this up, but I think that urgency has to be balanced against the fact that we have not yet had any contact of any kind with the Secretary and any opportunity to inform him of our enthusiasm of xenotransplantation, our concerns overall about safety, and to put the whole thing into a balanced picture, and that's what I hope we will do with our report. So my suggestion would be to inform him at this point in the format of a letter from the committee, a short letter basically with one paragraph describing, summarizing the need and the promise and the progress in xenotransplantation, a second paragraph summarizing the concerns about infectious disease risk, the need for caution and the kinds of regulation that we think are needed, and then a third paragraph specifically pointing out our concerns about this trial. I think something like that would help to succinctly express our concerns, but at the same time put it into the larger perspective.

DR. VANDERPOOL: And that third paragraph would involve we want to bring this particular issue to the attention at this time as we work on other initiatives with respect to the state of the science and so on.

DR. SALOMON: So just to put a little bit of a counter on that, my view is that we've spent as a country, through the FDA and now this committee, a tremendous amount of energy and effort harmonizing, both in this country and with Canada and Europe and others that have participated through the World Health Organization, a set of guidelines that albeit somewhat different in Britain and Canada and the U.S., at least it seems to me that there is a general consensus about the fact that there are some concerns and that there has to be an overarching regulatory authority for trials in xenotransplantation today. And again even though the details may be gray, the fact is that that should be in present. And when you send a letter like that to the Secretary, it's like okay, thanks, and I just don't think that's really the point here. I mean this is an advisory committee. Let's give him advice. You don't have to agree with me. It doesn't have to be my advice. But I think that the committee should give him advice. This is the problem. This is what we think you should do.

DR. ALLAN: I agree with Dan. This is a specific issue. It's not a global issue like embryonic stem cells or something else. We're dealing specifically with a potential risk that's in the immediate, not some theoretical in terms of what's going to be done. So from my perspective the letter would need to be very straight and say we have real concerns that having xenotransplantation clinical trials without any oversight or regulation of these in other countries may directly impact global infectious disease risks, and I think that's something that could be put in without us having to tiptoe because for us it's not a political issue. It's an infectious disease issue.

DR. VANDERPOOL: What you're saying, Dr. Allan, is thoroughly in keeping with what Megan said and what I first commented on. These are real concerns. We wouldn't say, you know, we just thought perhaps, we've considered the possibility of saying this humble word to you. I mean I think we need to put it in the language that's befitting of the occasion, but my only proviso would be that we would not use the word, we recommend that you. That's not the point. The real concern I think we're agreed on. So I think what we're challenged to do is to see if within the science committee if you all could begin to put together a letter that would say something about the promise, something about the very real concern that we have, and then we could circulate that, not only to other members of the committee, but to Dr. Groesch, and she could talk to other people who would be savvy in terms of how this should be worded for the Secretary. Lily?

MS. ENGSTROM: I just wanted to ask the committee at large if you're going to proceed with such a letter, I harken back to a question that Dan raised way back several meetings ago, and it was not a specific

case at that time, but the more broad generic issue. And if in fact the committee is going to raise this problem with the Secretary, it would be very helpful to put it in the larger context as well instead of singling out one particular experiment that's going on in Mexico right now because next week we'll see on some website or pick up a newspaper, and there's another experiment going on somewhere else. And two months from now who knows. So I think that the department would be appreciative of the insights the committee has to provide on the larger generic issue of how to deal with the kinds of problems that could emerge from trials without oversight overseas.

DR. SALOMON: Yeah, I think that's really well taken. The point that I hope came across, but let me just make it very clear, I'm not trying to be punitive. I think that anything we write in advice should be done positively and constructively. We can help Mexico. We can give advice to the Cook Islands. We can even put them in contact with people who will objectively monitor the trial. And I think in that way we reach out in a way to say, okay, if the Cook Islands or Mexico really feels for their own internal sovereign reasons that they want to do this trial there, then at least let us help you do it and do it safely. So I hope that everyone understands my intentions are positive and constructive.

MS. ENGSTROM: I also would like to add based on the articles I've read about the New Zealand problem, and I don't know how accurate they are. I'm going by just what the press has reported. Cook Islands doesn't seem to be very receptive to anyone intervening from outside, so as the science working group discusses this issue, one of the things that would be good to get I think some insights from you is how do you deal with an issue like that? Certainly we can offer assistance, we can offer advice, but if a sovereign country decides that it doesn't want -- you know, what are the kinds of precautions or measures one can take in such a situation? So that would be helpful.

DR. VANDERPOOL: Dr. Mendez?

DR. MENDEZ: I agree with most of what has been said. The only caution I would put on it is that we really don't know firsthand what is going on in Mexico and the Cook Islands, and before we castigate anyone or in a negative tone, I believe what Dan said is correct, that it should be an overall type of view, not particularly pointing to the two countries, but more also holding out a hand or a gesture of cooperation to see whether or not we can in any way help them or to find out what they have. Maybe they're far more advanced than we think they are. Maybe they do have some sort of regulatory aspect that's going on in some collaboration with some other country that we're not familiar with. Before we put too much of a negative twist on it, I think we have to find out firsthand or at least try to reach out and say, what's going on, and find out a little bit more about what they're doing rather than reading it in the AP Press or The New York Times.

DR. VANDERPOOL: I agree with that. We can look at the press releases we have in our notebooks for every conference and see the overstatements, the understatements, the misstatements that are being made in the media. So we need to proceed from a good information base. Maybe what this means is that although we maybe should structure a letter of some kind, maybe what we should do instead would be to have this as a major subject for our July meeting -- and really we've talked about this before -- and dig in at some depth what is being done across the globe and maybe have people in keeping with what Ms. Engstrom just said in the policy arena to apprise us of some things about what you can do and what you can't do with respect to foreign sovereign nations.

DR. BLOOM: I'd like to make a comment if I might. In the context of what you proposed to do, I also think it's important, not only that you consider what the United States has done in terms of our PHS guideline in terms of the FDA guidances, but the other countries, as you mentioned. An example would be the Council of Europe that is trying to draft a list of recommendations for a lot of countries. And you know what? They're not all buying it. There's discussion, there's give and take, and eventually you get

some consensus and agreement, but it's not straightforward, and it's not easy. And that's just Europe. There was an article that I got on e-mail when I went back last night that I forwarded to you because I know, Dan, that you care about these international concerns. The article was about four or five sentences. It was a press release about 12 porcine livers being transplanted in China. That's all Europe, and they're not going to cooperate with the OECD who's trying to form an international surveillance network. And so the problem is considerably broader, and I don't mean to sound political, but I don't think we're going to be able to police the whole world. So I think you need to consider all of those in the context. Also in Mexico in particular the idea that it's not just xenotransplantation that Mexico has offered that is something that the U.S. doesn't offer. Historically there are all kinds of medical and quasi medical treatments that have been offered. So it's actually an enormous issue.

MS. SHAPIRO: I remember talking at the first or the second meeting about how it might be useful for you to write letters to some of these other entities to kind of see what they're doing and how we might be able to work together, and in terms of the letter I thought that it might be a good idea just to kind of almost do a progress report to the Secretary. I mean he hasn't heard anything from us. This is where we are, this is what we're doing, and one of the issues we'd like to look at is this global concern issue, and we'd like to come up with recommendations for how we might as a world deal with this, and in the meantime you need to know about what we think is going on in Mexico.

DR. VANDERPOOL: I like that a great deal. I think that a letter in the context of a progress report makes a lot of sense. I hope that's captured by the recorders. Bill?

DR. SCHECKLER: Unless I'm mistaken, Lily Engstrom does report to the folks on the sixth floor in Tommy's office, and through the Deputy Secretary and so forth they're quite well aware of who we are and what we're doing. I assume that's one of the reasons that we have the various liaisons that we have here so that the FDA and the NIH and Secretary's Office and so forth, and so on, is all informed. We have a wonderful web page. We have more than enough information that the public can get a hold of in terms of what we're doing. I think maybe one of the strategies that might be useful -- and Lily, I'd be interested in your comments on this -- would be to have our Chair visit, have ten minutes of face time with Tommy, to present a letter rather than just send something written. Seems to me, knowing Tommy as I do, that that would be a useful strategy in terms of informing him of things, and this is much larger than the issue of some experiments south of the border. The whole international xeno tourism, I think Dan's word, is a much larger issue, but the larger issues are all of the things that we've been dealing with for the last four meetings. So Lily, I'd like to know what's the chain of communication, and would a strategy of a little face time, as hard as it is to get, work?

MS. ENGSTROM: I'm the first to tell you getting face time is a challenge because this Secretary believes in getting personally involved in so many issues across the board, and of course, bioterrorism is among the top of the priorities for the department right now, and that's no secret. I think that if in fact the committee as a whole would like to have Harold meet with the Secretary, I'd suggest a couple of things. One, that you agree on the kinds of things that Harold should be discussing with the Secretary, and if we're talking about xeno tourism, what specific suggestions you have to make because it's a daunting challenge. And as Eda mentioned a few minutes ago, we all recognize the risks that are associated with countries and entities that are doing xeno without regulatory oversight, and I think that one of the things that we need to recognize is if we were in fact to do something, would that actually take care of the problem or in large measure address the problem if we don't have the cooperation of others in the matter? Secondly, I can certainly request time on the Secretary's calendar for Harold. He has his own scheduler, and we'll just have to work it from there and see whether or not we can in fact do that.

DR. SALOMON: Lily, could you comment just in terms of political strategies here? My view tends to be to do something rather than talk, and that's a personality. You guys know me by now. So the way I

would think of it is here we have a special relationship with Mexico, we have the North American trade agreement, there is xenotransplantation going on right across the border an hour from my house in terms of the shark xeno transplants as well as a set of rejuvenation clinics in Tijuana. I mean it's not a minor issue. This is something that I think, as I said, we have a special relationship with Mexico, so that one strategy would be to say, look, we know there's this whole complicated, difficult and sensitive global issue. How about something that's focused, constructive, positive and done with something that's right on our border? That's one strategy. And that could be done now. I agree with you though if we go on to a bigger picture like let's go advise a series of steps that would deal with the global issue, not that that's not critical, but I don't think we're ready to do that. What do you think is the best political approach?

MS. ENGSTROM: This is a can do kind of Secretary too, so I would strongly suggest that if Harold were to meet with him, that the committee have some specific recommendations in mind because he will surely ask, okay, all right, I understand the nature of the problem, and certainly I realize the risks that are involved. What does your committee recommend? What should we be doing?

DR. VANDERPOOL: I completely agree with that. From what I know about the Secretary, furthermore, I also know the Secretary is savvy and very concerned to make sure that his relationships are good with the White House. So there are some politically sensitive aspects to President Bush's treasuring his relationship with Mexico. So I think that we would need to be very savvy and careful about making comments or statements as if the finger is pointed toward Mexico as the place where the infections are occurring. What I would suggest, I think we need to close this discussion, although what we've done has opened up a four-hour discussion, and say that the science committee group, could you put together a couple of paragraphs? Mary and I and whoever else would like to join us can say something about progress, something about the promise, something about our cautions and worries, and then the fourth item in the letter -- and we're talking about very brief paragraphs here -- would be we would suggest the following, and that might have to do with our needing to have better communication with other nations and to encourage international efforts to the ones that are already underway. We can decide what to do. Does that make sense? I mean the science group needs to put together your two paragraphs. We need to talk about the progress, and I'll stay in contact with Lily and Mary and others, and we would circulate whatever we come up with here by e-mail before we take any action on it.

MS. ENGSTROM: Harold, can I add a comment? I'd like very much to endorse the remark that was made a few minutes ago that we really do need to find out a little more about the Mexico situation, and I think that armed with more information, I think we can in fact provide better advice. So I think that the task of the science working group would be to try to find out a little more about that particular situation down there and what the dimensions of that particular project are and what does it include and how it's being carried out, what kinds of patients are involved, what kind of result if any there is.

DR. VANDERPOOL: Dr. Chapman?

DR. CHAPMAN: I'd like to suggest to the working group this committee's responsibility is to advise our Secretary of Health and Human Services, but when you get to the point in the letter where we're advising him on how he should act, it's perhaps worth exploring carefully options about what that should be. I'm wondering, for example, what is the role of the Pan American Health Association in this kind of situation, and if you're talking about advising the Secretary to go to someone, should you be advising him to raise these concerns with that body or some other body as opposed to. So I think in addition to exploring what are the facts about what's going on in Mexico, you want to think carefully about what are the multitude of options and appropriate processes on how you advise the Secretary to act and to whom you wish him to convey concerns.

MS. ENGSTROM: I think Louisa's point is well taken, and it echos basically what Eda said earlier,

which is we can't solve this problem alone by ourselves, just by its very nature. Therefore, if we are to proceed as the U.S., there are going to be a lot of collaborators and partners we need to have in this effort, so that should be taken into consideration as well as the working group and eventually the parent committee decides how it wants to approach it. And whether we're talking about the immediate problem next door to south of us or we're talking about the China situation that Eda just brought to our attention or any others that might be emerging, the question is as a U.S. government at law, there's no way we can lick this problem, so what are the kinds of measures that we can take in collaboration with others, and who are the others that should be in fact involved with in this partnership?

DR. VANDERPOOL: My immediate response to what you said a moment ago, Lily, about okay, now, what do you suggest, I was afraid you'd ask that question. We want to bring this to your attention, and it's really up to you and others and your advisors to decide what to do about it. Our own committee has thought along the following lines, but we see ourselves primarily as offering the kinds of information that need to be worked off in an astute way that you and others are responsible for doing. I think we need to be very careful about offering specific advice that dips into the political arena. We'll see where that goes. Drs. Allan and Sykes?

DR. ALLAN: I was just curious as to whether if this issue is important enough that the science group wants to deal with this today, the question I have is does the other group want to be involved in this discussion? And maybe we shouldn't have breakout sessions. We should have just a continued session with everybody to discuss this.

DR. VANDERPOOL: The informed consent group has done a lot of work, and we're moving along well. We're dipping into the section of the public comment, and we won't short-change that session. And yeah, we're dipping into our time of our working group, but I want to spend some time with our working groups because the working groups have lots to do in terms of what form our reports are, where our heads are. This is a nice time to seize that opportunity for your group and for our informed consent group, who really needs to do some head to head work and share what we've come up with. Dr. Michaels?

DR. MICHAELS: I was just going to propose that during our outbreak group that we can start working on that letter that we can then share with the rest of the committee by e-mail.

DR. SYKES: I'm not sure that we're actually focusing on the only issues regarding this trial. I'm afraid that we may not yet have all the information we need to be able to specifically come out about this trial as I think about it. I think the issues go beyond the infectious disease risk, and the infectious disease risk is obviously a huge one, and this xeno tourism is a huge concern, but as we've just heard, this is going on elsewhere as well. So I'm not sure why we should focus on this trial in particular with regard to the infectious disease risk, particularly as we don't really have the information as to who is following these people for infections. I've been told by others, and I think Dr. Zhong said as well, that in fact there is some follow-up being done, but we know very little about how that's being done and by whom. So I'm beginning to rethink whether or not this specific trial should be highlighted in our letter with regard to infectious disease risk. I think the broader concerns about this trial have to be discussed by the committee as a whole because they concern ethical issues. Here's a situation of a developed country apparently not allowed to conduct a trial in its own country doing it elsewhere. They're using a device, implanting it into children. We know nothing about the kinds of informed consent that were used on those children, and in my view the risk to benefit ratio, not only risk to the children themselves, but to society, is extraordinarily high. There's no science to back up the potential benefit. So I think there are enormous ethical issues that we need to say something about with regards to this trial in particular, but from what everybody's saying, it's the infectious disease risk that we want to bring to the attention of the Secretary. So my suggestion would be not to particularly highlight this one, but perhaps mention it as an example that we're concerned about.

DR. VANDERPOOL: I think that's an excellent summary. So I think where we are is two things. One would be to seek to put together a brief progress statement, a brief promise statement and a cautionary concern paragraph that doesn't particularly single out Mexico, although if some verbal exchange occurs, that can be used as a for instance with the proviso that you and Dr. Mendez have mentioned that we're not altogether sure what is going on, but it seems to be of significant concern, as are other concerns across the globe. I hope that summarizes where we are. The second point would be that it seems to me imperative that this issue of what's happening on the international scale and where we are in terms of overarching regulatory ethics commissions and what's happening in terms of experiments in other nations would be an important agenda for our next meeting. Are we agreed with that? Now, it's always possible that in tomorrow's newspaper something will come up that will scoop that idea, but right now this is certainly seen as that. Thanks very much. We've accomplished a lot in a brief period of time.

Now we have some highlights of recent articles and meetings. I would like to do some of this at this time. First off, we have some video excerpts from an interview with Jim Finn, and he wants to make a couple of comments about that. And so Jim, let's proceed with your video and any comments you'd have about what's occurred vis-à-vis your experience.

Agenda Item: Highlights of Recent Articles Regarding Attitudes Toward Xenotransplantation

MR. FINN: Thank you, Doctor. Good morning, everyone. I'm a xeno transplant recipient, and I've been interviewed by television lots of times. I brought two videos with me that I'd like to share with you. Mannie?

(Video played)

MR. FINN: The next video is really two videos in one. The story within the story was taped about two years ago for the Discovery TLC channels, and it's part of the tape. This was made on Oprah just before Christmas.

(Video played)

DR. VANDERPOOL: Jim, any comments for the committee at this time? Thank you. The only mistake we made, Mary, was not have champagne to pass around for our movie stars. We have Julia Greenstein also and then Jon and of course our lead star.

MR. FINN: An international cast, yes. Another thing I want to say is that Oprah is a lovely lady. I was on the verge of tears when they taped this. It was very emotional to be involved with a studio audience and taped. Her program runs as what you see is what you get. There are no rehearsals and no retakes. That was the show as was taped. Thank you all.

DR. VANDERPOOL: Thank you, Jim. Thank you so much. Okay. Now I think we're going to have to move to public comment. The problem is I really would like to hear the reports of Karren and Robyn on Canadian public consultation and on attitudes of patients waiting for transplantation. What do you think? I mean, Karren, can you say something about this report, very briefly, and Robyn, you have something to pass on?

MS. SHAPIRO: We don't have enough time.

DR. VANDERPOOL: Okay. So they have reports to pass out to all the committee

members.

So to move along to public comment, you do have a handout from Ellen Meyer, legislative consultant, and this has to do with the coordination organization, North American Coordination Organization.

And then we now have, we have two public commenters, Kay Gregory and Celso Bianco, who will comment after Dr. Dayton gives his FDA guidance draft -- draft guidance to industry talk, because this has to do with -- their two comments have to do with blood products.

But are there other -- now, first, let's have Dr. Amy Patterson speak, and then any other public members who would like to make comments or ask questions, feel free to do so.

DR. PATTERSON: I was wondering if the FDA could provide some clarification on the letter to industry for the ART procedures performed using animal fetal cell layers. We're a little confused about the position to require IND henceforth for this procedure and yet the -- it was still a little bit vague, at least in my mind, and perhaps in the mind of others, about what was being done with the progeny of these procedures for the past ten years. What kind of guidance would be offered to mothers and physicians? I realize to some extent it's going to be on a case-by-case basis depending on the cell line used for the procedure. But because it does, number one, seem to be a decision that has some profound ethical, legal, social in addition to epidemiologic implications to now look back to say that the progeny of these procedures will -- are perhaps at risk for a zoonoses, I was wondering if you could shed some light on exactly how people already born of this process over the past ten years would be counseled, what the agency thinking is on that?

DR. BLOOM: Well, I think we had, at the beginning of this discussion when Dan asked what we were going to -- whether we were asking the ART concerns to go -- assisted reproductive technology -- to go back and contact people. And this letter took a while in coming because we gave a great deal of thought, a great deal of discussion all the way up to the department OMB on how to handle this and to get approvals. And we're trying to be sensitive to the women who have had this procedure in the past or the children that have been born to it, but we're trying to protect the public health. And the idea is that we are asking that people call us, and yes, it would be a case by case, and yes, it would advice. We are not going to be able to force individuals to be monitored, but they have a right to know that they ought to be monitored. We would also advise them about the blood donor deferral. We would advise them to be vigilant for any potentially unknown reasons for infection, and to keep us informed. There will -- at least right now we do not have plans to include people that have already been treated, and we consider the mother as the recipient.

DR. PATTERSON: Well, that was one of my questions, whether, if you're making a decision to regulate this under IND because you think that there's a public health risk as a byproduct of the procedure, whether it's worthwhile to gather data because you already have progeny born as a product of this, so that's a source of information to help you quantitate the risk. And it was unclear whether there was going to be any effort to actually proactively contact these people or whether it's a passive type thing that you're making the announcement and if mothers of these offspring happen to see it, they call in, or if the physicians choose to contact them, then there will, perhaps, be a way to

notify these people and follow them. But that the chain of events and how this information is being conveyed to the people most affected by it seemed unclear to me.

DR. BLOOM: I think what you've said, though, is -- it doesn't sound like it's unclear. We are not going to go back specifically and contact people.

DR. PATTERSON: Okay.

DR. BLOOM: Yes, they have been treated for probably as much as ten years. Is that enough time to get a good retrospective look? We really don't know. We're asking that specimens be maintained for 50 years because we don't know how long the period would be from when treatment occurs to the potential for an adverse infectious event. It's a much more delicate area of research than many that we've dealt with. Part of the reason for waiting to get into it until this current time is in addition to the xenotransplantation definition, which covers this area of assisted reproductive technology, we also have our tissue regulations that speak to the idea of donor eligibility, including an assisted reproductive technology.

So it's kind of a gradual and concerted progression. Concerted may not be the right word, coordinated progression to try to be sure that this area proceeds safely. We would prefer that people not do it from now on unless it's under IND, which will give them better quality control from now on. Just because things have happened in the past doesn't mean you can't make it better in the future.

DR. PATTERSON: Sure. Thank you.

DR. VANDERPOOL: Dr. Michaels.

DR. MICHAELS: I just want to, just for clarification, so if a mother does see this on the web site or wherever, and she were to call and she has a child, then what you're offering them is counseling. And are you offering them testing depending on what kind of fetal level, what kind of fetal line was used like SV40 testing? I'm still a little confused, sorry.

DR. BLOOM: I don't think -- you mean for like vero cells? We're are not going to offer them advice, we are not going to offer them testing at this time.

DR. VANDERPOOL: Other comments? Other members of the public would you like to make comments or ask questions, please come to the mic. Identify yourself and proceed.

PUBLIC COMMENTER: My name is Andy Breslin, I'm just a concerned citizen. There are a lot of things I could comment on, but I just wanted to comment on one thing that I just picked that disturbed me the most, which was the comment that Dr. Collins made that baboons were as uncooperative as his three-year old. And I think there's room for debate about the many scientific issues involved in xenotransplantation and there's a lot of room for many different points of view about the many ethical issues involved. But it's really the height of insensitivity to hold the animals that are involved, animals that are captured, killed and caged for human benefit in disdain because they are not cooperative. And I wonder if anyone in this room were to be taken and be subject to experiments that were going to lead to their inevitable suffering and death

how cooperative they would be with that. And I think that to regard the baboons who are being sacrificed for this in anything but gratitude and apology, but rather to hold them in disdain, is frankly insensitive and really disgusting. And it's difficult to take seriously the claim that the committee has animal welfare concerns in mind when that sort of commentary goes without comment. Thank you.

DR. VANDERPOOL: Thank you. Other public comment? Dr. Collins.

DR. COLLINS: Thanks, Dr. Vanderpool. I certainly take your points to heart. And the comments yesterday certainly were a little cavalier. I think in life we make choices. One of those choices is in the medical field, for instance, the decision is made do you believe that using animals for research will better humankind, and that's a decision that I have made. Mr. Berger, on the end of the other committee, has a disagreement with me about that, and it's a fundamental disagreement. I think the greatest thing about America is that we can have these fundamental disagreements and still talk about them. I take your comments to heart, but wanted to let you know that I do come down on the side of using animals for experimentation to further human health.

DR. VANDERPOOL: Thank you, Dr. Collins. Yes. Mr. Berger.

MR. BERGER: Harold, I might add something since this came up yesterday from Dan's comment. You know, it might be useful to have a speaker at the next meeting that really dealt more directly with animal welfare issues. Michael did something about housing of animals. The guidelines, when they were issued, have long segments about animal care, but it was more for the protection and infectious disease risk that had little to do with actually the welfare of the animals, an attempt to reduce the numbers that were being used
Or an attempt to provide better living conditions for the animals. And it might be useful to have a speaker that would discuss that in a little bit more detail at the next meeting.

DR. VANDERPOOL: Also, as I recall, in our very first meeting, Dr. Lilly Russow spoke about animal welfare issues. And we have not really talked about those issues since she raised some of these concerns.

So we'll certainly take this under advisement as a topic in which we can have presenters on both sides of the issues that our first commenter has made, along with the question of having different values that Dr. Collins has raised, certainly extremely important debate, and with different values being explained on each side. Now at this point -- yes, Lilly.

DR. RUSSOW: Yes. I'd like to comment on that since I talked about that at the first meeting. I think that I probably occupy a middle ground between some of the factions here. Unlike Alan Berger I agree that there are important advances to be made through research on animals, that we couldn't do the things that we're doing today without such research.

However, I also agree with him that animal welfare has to be at the forefront. You cannot waste animals doing unnecessary research or research that's just sort of pie in the sky, let's see this and see what happens, and you have to make sure that the animals are being taken care of in the best way possible. I think both of those are important. I don't think Dr. Collins would disagree with any of that.

And so I think that while animal welfare has to be at the forefront of all of these discussions in any decision about how and when we use animals in research, I do think that there is strong argument that we need to use animals at this stage, with respect for the animals, with absolute care for the animal welfare. But there's no way that we can do the kind of research that we need to benefit human health, to gain basic scientific knowledge that's going to be important down the road, and in fact to benefit animals in some cases, not necessarily with the xenotransplantation, but with other sorts of animal research.

And I think everybody in this room would probably agree that if there were a way to get those results without using animals, yeah, let's go for it, but right now we don't have that capability. And so all we can do is take care of the animals and look out for the animal welfare to make sure that their lives are not sacrificed in vein and still go forward with animal research. And I take that to be a respectful way of using animals. Not the ideal way of doing research, but we don't have an ideal world right now.

DR. COLLINS: I certainly concur with Dr. Russow's comments. Truly we all love animals here and I have pets. The point that she made, and I totally agree with, we shouldn't be wasteful. Their upkeep and how they are taken care of should be as close to their natural environments as can be made possible, although that's not always possible in laboratory environments.

I do agree with you that we shouldn't use and waste animals. I agree with Mr. Berger there, too, it's very important we're careful. That's why at all universities before you're even able to do experiments utilizing animals you have to go through very stringent training programs. The people looking at your protocols will come by and look at the animal husbandry, et cetera. I didn't mean to sound so cavalier yesterday.

DR. VANDERPOOL: Reminder. With these comments if we have this as a segment we can have -- not only -- we will have a fair representation of the speakers, including the position that Dr. Russow has laid out in terms of mediating positions also.

At this time let's go to our breakout sessions. And in terms of timing, we're going to finesse the break, find ways to break on your own, so to speak. So we will go from -- at the time we can go to our respective rooms. Do we know where those are Mary?

DR. GROESCH: Yes. I want to point out that the breakout sessions, there will be concurrent meetings of both working groups. One is on informed consent issues in xenotransplantation. That group will be meeting just across the way in the room -- the door is open, I can see it from here. And then the working group on state of the science in xenotransplantation will meet in here as we did last time.

Members that are here are welcome to sit in on either of the working group meetings or go back and forth. And we will still take the two-hour time period for the working group session. When you come back we will have your boxed lunches that will be waiting for you and you can eat those during the reports of the plenary discussion of progress reports of the working group meetings. For members of the public we'll have a little more substantial break for you since we're not breaking for lunch. I think there's going to be granola bars and fruit and sodas for you, to make up for the fact that we're not giving you a lunch break.

So we'll come back here, say -- it's 10 after 10:00 now, we'll come back here at 10 after 12:00. We'll eat lunch through the progress reports, and then we'll start again hopefully on time around 12:40 with the discussion of the FDA guidance. Sound like a plan?

DR. VANDERPOOL: Great. Thanks.

(Recess taken at 10:09 a.m for concurrent breakout sessions during which the SACX Working Groups convened.)

(Resumed at 12:21 p.m.)

DR. VANDERPOOL: Two members of the SACX committee have requested that we make comments about the Canadian Consultation on Xenotransplantation statement, and I think it is important that this meeting not end without some reference to that. So Robyn will make some summary comments about that. We also have Eileen Tackenberry from Health Canada, she wishes to make a comment. And then a very brief discussion -- and so we can be enjoying our lunches as we do this. And then we continue to finish our lunches as we move then to the plenary discussion regarding updates on what the working groups have done.

MS. SHAPIRO: I'm certainly not an expert on this and there are people here who are, so take what I'm going to say with that and I'm happy to be corrected if I say anything wrong.

The Canadian Consultation on Xenotransplantation, a little bit of the background. In 1996 Health Canada started to consider potential regulatory guidelines as I guess we're doing, in part for clinical trials, and it appointed a multidisciplinary xenotransplant expert working group to consider many of the same issues that we in fact are considering in our work here. And it came up with some proposed standards and put them on a web site for comment, but then started to think that they really should get more input from the public. So in 2000 Canada Public Health Association formed a public advisory group to do this public consultation and answer some of the questions about how and whether to proceed with xenotransplantation in that country. There's seven recommendations, and I would urge you to take a look at them if you're more interested than the three-minute summary.

That this group released in January 7th of this year the most controversial, perhaps, and the most prominent being that Canada not proceed with xenotransplantation involving humans at this time, as there are critical issues that first need to be resolved. There are other good things like we should be educated, we should do prevention, we should enhance organ supply, other ways and so forth.

The process itself involved two models. One was the open model designed to promote input from everybody in that country through surveys and letters and a web site survey. There's a telephone survey of about 1500 Canadians, a mailed survey, about 3700 were mailed with a 5.8 percent return, and web site surveys.

There's also a representative model which drew opinions from specific individuals who are panelists really at six regional public fora. And their discussion was preceded by some presentation by experts on all the topics that we've talked about here, infection

control, FX law, so forth.

There's a wonderful critique that's also included in your packet written by Dr. Wright, who is actually with us today. I'm just going to go over a couple of the highlights -- some questions that are raised by this consultation process.

First of all, the method with -- in my mind, an overarching question being that, the question was too broad. It was not broken down in categories of xenotransplantation, which may indeed have different levels of associated public and personal risk. There was great variability in the data, perhaps, due to variability of the experts who, again, made presentations to these panels prior to their weighing in.

There were questions about the adequacy and the integrity of the response rate. There were very few hits on the web site. There was no assurance that people didn't respond more than once. So people who are particularly vested with this issue, perhaps, answering more than once. No assurance that only Canadians responded to the web site even though that was the directions.

And finally, there are, in my mind, some questions about the validity and/or the usefulness of the results in any event. For example, just one example, apparently two-thirds of the panelists supported xenotransplantation as a potential future of clinical modality if its safety and efficacy can be demonstrated. But, obviously, to demonstrate that we would need to allow for some well regulated clinical trials.

So the usefulness of the data and the recommendations, even if we allow for the fact, which I don't, that the methodology was okay, there are questions with that as well. Any corrections, Dr. Wright? Anything you have to add?

DR. WRIGHT: No, you summarized all my opinions, as well.

DR. VANDERPOOL: Okay. Is Dr. Tackenberry from the health center here? Thanks.

DR. TACKENBERRY: Just one very short comment I wanted to make. I'm with Health Canada, particularly it's now called -- it's renamed itself, it's the Biologic and The Genetic Therapies Director, which is comparable to the CBER portion for the FDA. And for many years, as you summarized, we have been struggling with many issues as you and others worldwide have been.

My only comment was really with regard to a sentence that's on the last page of Dr. Wright's article, where he has said that xenotransplantation clinical trials should be -- commenting that they, sorry, that the directions of when and under what circumstances xenotransplantation clinical trials can be allowed to go forward cannot be decided by public consultation.

I would agree that public consultation in and of itself is not going to be and never was -- the intention was never to make it, you know, the sole or perhaps even the major determinant of Health Canada policy in this regard. It's one of many things that are being considered. And this, you know, we'll engender more public discussion, which is obviously a good thing.

DR. VANDERPOOL: Thank you. Any comments from anyone around the table on this consultation? Thanks Robyn for your brief summary that you've given for the committee. Bill Scheckler.

DR. SCHECKLER: I was interested in reading Dr. Wright's comment, with which I agreed with, having seen the Canadian report. I agree entirely with what Robyn said. In my department of family medicine there is a great deal of work on qualitative analysis and focus groups. The strategy used for the focus groups in this case across the country was indeed not anything that would pass muster in any kind of IRB or in any kind of study, scientific study that was done, because the groups that were conducting the focus and providing the information weren't standardized in any way.

As far as the survey with a five percent return rate, that's laughable and should be ignored. I think only marketing firms look at return rates that low and find some value in them. But in terms of any kind of standard scientific sampling, that is meaningless, and the same is true for the web site because the numbers are so small.

There is the implication in the report that the initial survey, which was a more Gallop Pole type of standardized survey, that the people didn't know what they were responding to and, therefore, their opinion we'll ignore has to be fixed by these other methods which were much better. It may very well be that the people weren't -- because the statement or the question was so broad that it would be impossible to really answer it.

So I think in terms of public input the whole thing was flawed. And if it was a public health association that did it, I'm concerned about that. I'm concerned about their methodology. And I really -- I think if Canada wants to get their opinion of their public they are not there yet.

DR. VANDERPOOL: Other comments from the committee? Jon Allan.

DR. ALLAN: I mean, I read it and I thought it was interesting, and I don't know that -- I obviously don't know how these things are done or anything, but the only thing I thought was interesting was at least Canada had tried to get some public feedback on xenotransplantation. Maybe it's flawed and maybe it's, you know, shoot the messenger. But it seems to me that in the United States we don't tend to do that, you know, we get CNN or Fox poles on something, and you get one question and you get the answer or it's in the USA Today poll or whatever. At least Canada tried to get some sort of feedback on what the public thinks about the entrant. It may be fatally flawed. The United States, we don't do that, and sometimes it backfires. I mean GM Foods has sort of backfired to some degree because of the fact the public was not informed properly about the science.

So how do we in this country deal with the fact that if xenotransplantation does move forward that we don't want some sort of backlash because the public wasn't adequately informed.

DR. VANDERPOOL: There's probably some connection, Jon, between what you and Dr. Scheckler just mentioned. You're saying congratulations or praise for doing something, and Dr. Scheckler is saying, well, look, you did something, but what you can draw from this is flawed unless you use very accurate measures of community

opinion.

Any other comments from committee members? Let's move quickly then to -- thank you. Let's move quickly to the reports from the working groups, and we can proceed first with the report of either group. Who is going to report out for the Status Science Group. Jon, is that you or Megan?

Agenda Item: Plenary Progress Updates on Working Groups

DR. ALLAN: I think we should start with the letter. We spent most of our time talking about this letter.

DR. SYKES: Yeah, there was a great deal of discussion about the content of the letter and what we came up with was -- I think most of us agreed with an initial paragraph introducing ourselves, stating that we're working on a report, but stating up front that we're writing to advise him of a concern that we believe deserves immediate attention. And then saying that we are working on a report and a few words about the promise and potential impact of xenotransplantation.

Then a second paragraph saying, however, the enormous benefit of xenotransplantation does not come without significant potential risk in public health.

Then a paragraph explaining the infectious disease risk in fairly simple terms, as well as a brief mention of the fact that various government agencies have been working in recent years toward the development of safe policies and practices to ensure the safety of the recipients and the public at large. Also pointing out that there have been interactions with bodies from other countries in this regard. There are details that we still haven't worked out as to the language and content of some of these paragraphs.

Then the third paragraph will contain language basically explaining our concern, that there are countries performing xenotransplants without guidelines that we're aware of. And basically we spent a lot of time trying to come up with specific recommendations or specific bullet points that we are asking the Secretary to ask on.

And there were two that we agreed on as requests -- as action items for right now. We asked him to convey our concerns via the executive branch of the government, and to use government-to-government interactions to try and convey these concerns to the international community.

Secondly, we would like to ask him to use the resources of the Public Health Service to retain more information and have these agencies then inform SACX on what they have learned about these activities abroad.

There are many other specific recommendations that we think would be best left to the report that we give to him, such as -- well, actually, somebody brought this up later, and maybe this is something that deserves more discussion now, is whether we should ask now for some sort of a warning to go out to the American public that going to Mexico, for example, for an eyelet transplant for their child is going to potentially put the child and the public at risk, and that there are guidelines regarding xenotransplantation, and we don't know that these are being followed in this setting. That's something we didn't discuss much at length, but, that third point, but perhaps we should get some comments

on that right now.

DR. VANDERPOOL: Thanks very much. I'm glad that you moved on with all due speed on the letter. Did you all talk about your longer position paper you want due and if so, when you would want to have that done?

DR. SYKES: You mean our report, our larger report?

DR. VANDERPOOL: The actual report.

DR. SYKES: We didn't actually come up with a time frame. We spent a little time discussing the format and I think we agreed that there should be a one- to two-page executive summary at the beginning, sort of bullet points for the Secretary, summarizing the report. And that the report as a whole should aim to not reiterate what already exists in other reports, but rather to focus on issues that have been missed in previous reports or that have come up since those were drafted, and come up with specific, same with the science also, point out what's new and what has come up most recently and what the current problems are and so on.

We have actual outlines for the various parts of the report that we could take you through. So we divided it up into three sections. The first section includes an introduction. We'd understood that you have something already written that we could draw on for the introduction and then add to that if it's not already there. The need for more organs. The potential economic and public health costs of the organ shortage. The potential impact of xenotransplantation on public health and alternatives to xenotransplantation, where xenotransplantation fits into the big picture, as far as public health impact goes.

Then the second section will be on the science of xenotransplantation, and that's divided into a description of the obstacles, followed by descriptions promise of new technologies, a list of areas that we feel need a lot more investigation, and some recommendation hopefully with suggestions for priorities. And we've divided each of the exceptions into a number of areas, and I don't think I need to -- I don't know if you want me to run through the details of all those sections right now.

DR. VANDERPOOL: No, I don't think so. Because we do have this special guidance of industry section with the FDA. So why don't we report out --

DR. SYKES: Sorry, we weren't finished though. There is also the infectious disease section is the third section, and Jon can probably report on how that is coming so far.

DR. ALLAN: Just to say we're just starting to work on it, so it's in its infancy, and we're just structuring it now and we're going to be e-mailing back and forth, so hopefully we'll have something moving along by the next committee meeting.

DR. VANDERPOOL: Great. In terms of the Informed Consent Working Group, we had a number of documents and suggestions to hand around and dealt with the different parts of what we see as our position paper. An introduction that says there are a lot of ethical questions and the informed consent is one of them, followed by a brief section on the values and functions of informed consent grounded in ethical and legal and other values.

And then a third section on the issues regarding informed consent that are unique to xenotransplantation. And that would, for example, would be risks to the subject, risk to intimate contacts, responsibility of participants once they enroll, including the fact that they are responsible not to withdraw from being monitored once they consent to receive a procedure. And then the second -- followed by a section on the process of consent. The need to present, we'll have ongoing and staged discussions to have both physicians and nonphysicians involved in the process.

And then that process section followed by a section on the content of consent forms. We've tried to draft out -- we have drafted out initial document of what all the topics and subtopics should be, and to draft this out both in terms of comprehensive coverage, but also in terms of what, what arrangement would be most given to the subject's comprehension and understanding of what the information is.

And then a final section on special issues of consent, voluntary participation, but yet responsibilities to stay to be monitored, and some of the penalties that could be given to public health authorities for not maintaining those responsibilities.

Part of what we have to deal with is that some of the -- certainly organ transplants will call for some special changes that may have to come from the Secretary of the Health and Human Services himself.

So we've got an outline. We've got two or three sections in draft form, pretty thorough draft form. At the end we all agree as a committee that we will have a full draft document a month before our next meeting, and that that would give us a time to go back and forth with respect to having a more refined position paper to present to the meeting, to give to the meeting, report out and discuss for our meeting hopefully this coming July.

Now, let's open up for a brief discussion of what each paper is to be. But I wanted, before we move to the FDA draft guidance to industry, which we have to deal with, for Jon Nelson, who is of course our representative from Health Resources and Services Administration to say something about how these papers would relate to the Secretary and what responsibilities we have and what processes might need to occur in order for us to release statements, brief document, full documentary reports, get them published, have news conferences or whatever. He's not going to address all those issues, but Jon has some wisdom to give us on where our reports stand vis-a-vis informing and, perhaps, at points receiving clearance from the Secretary.

MR. NELSON: Wisdom. Rather than address all of those maybe I can just -- and I will be working close with Dr. Groesch on how to do this.

Just some context, the Health Resources and Services Administration has sort of a sister advisory committee, and I think probably most of you know that within the department there is something between 600 and 700 advisory committees. Just so you have some idea about that.

The committee that we manage is the Secretary's Advisory Committee on Organ transplantation. You're fortunate because Dr. Crone at the other end here is on that committee as well, so there is some overlap. The charter of that committee, and it was

constituted roughly about the same time as this one, it revolved out of a report from the Institute of Medicine back in 1998, and was constituted and put together in 2000, the year 2000. Initially had about 20 members, now has about 41 members. Its charter is broader than the Xenotransplantation Advisory Committee. It is charged with advising the Secretary and it's also, I would argue, somewhat higher profile in a sense because it is arguably more political and focuses on policy matters instead of science matters, and I think you're fortunate for that. But it looks at advising the Secretary generally on transplant, organ transplantation policy. And, secondarily, although this has achieved and gained maybe a greater credence because of the Secretary's strong interest in the donation, to look at organ donation initially as well.

It has a regulatory responsibility to look at and advise the Secretary on allocation policy. And as most of you know, that was really a hot spot over the last several years on organ allocation policy.

But the Secretary, what he has chosen to do, and I think it has some great merit, is to use the resources of that advisory committee to look at a lot of the public policy issues derived from the donation side, and there are a number of them that are in the lay press as you all know, living donation, nonheartbeating donors, what are the ethical issues.

So I think there's a great deal of parallel in this committee and this strong interest, maybe a subordinate interest in increasing donation, but to have the two groups coordinate their efforts and to provide sort of a common front of the Secretary, because at least in our -- and we've only had one meeting in that advisory committee, which was held last fall, and it will be submitting to the Secretary comments or recommendations, and I can't tell you when, but specifically dealing with federal organ donation policy.

But because of the interest and the parallel interest between this committee and that, it probably wouldn't be a bad idea to at least coordinate those two so that the recommendations that derive from this group on the implications of xenotransplantation is potential in the future and what that future is, whether it's five years or, at least for me, 15 years ago xenotransplantation was ten years off. And we all know that it is here as well as ten years off. But to coordinate that presentation, because I think collectively the Secretary will pay a lot of attention to transplantation matters if they come from the two groups. I say tongue and cheek 650 or 680 advisory committees, but he will pay close attention to these two. He did attend the Advisory Committee on Organ Transplantation. I think we have the two chairs, Nancy Azar (phonetic) from San Francisco is the chair of that advisory committee.

But you might want to think about, for your own purposes, with Harold and Nancy going together, thinking about what kind of a message the two groups might have. I think it would give you greater traction. And we can work also within the department about how to get the recommendations with Dr. Groesch through the department, to the Secretary, and ultimately have an active on it, which is what you want.

DR. VANDERPOOL: Thanks so much, Jon. You and I need to stay in close communication. And those of us who are co-chairs for the two working group documents also need to stay in communication with each other and with Jon, because we do have the, not just the political, but it's the social time frame realities, the timing realities that go with how we can be most effective. And thanks for those comments and we received some also from Lilly Engstrom's in the Secretary's office, and we'll

also stay in contact with her. Fortunately, we have someone situated full time in Washington who can help coordinate this in our executive director, Dr. Groesch. So we'll stay on top of this and we will time things as best as we can and we'll seek to be anything but naive about how we should proceed from here.

Agenda Item: FDA Draft Guidance for Industry.

DR. VANDERPOOL: Okay. Let's move to the final session of the meeting, the FDA draft guidelines for industry precautionary measures: To reduce the possible risk of transmission by blood and blood products. And we'll begin with a presentation by Dr. Andrew Dayton, followed by two public comments from Kay Gregory on the one hand and Dr. Celso Bianco on the other, and then open it up for questions.

DR. DAYTON: I'm Andrew Dayton, I'm in the Office of Blood Research and review at CBER, and we are charged, amongst other things, with protecting the safety of the nation's blood supply. And our approach towards the xenotransplantation is to come out with a guidance document, which is now out for the second time in a draft format, suggesting steps that the blood industry should take to protect the blood supply from possible problems that might arise from xenotransplantation.

Now, certainly this committee doesn't need to know the definition of zoonoses, but we do define it in the document to make it clear to the industry. I'm going to try to abbreviate this talk so you can move on as quickly as possible.

We also define xenotransplantation as any procedure that involves the transplantation, implantation or infusion into a human recipient of either live cells, tissues or organs from a nonhuman animal source or human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs.

Now, that is kind of an exhaustive definition. And the reason we go to such lengths to define a term like this very clearly is that we will be involved in asking blood organizations to take certain actions and take certain preventative measures, and we need to define our terms fairly carefully to define for them what they have to do with different categories of xenotransplantation products or the recipients or their close contacts.

Now, xenotransplantation products include live cells, tissues or organs used in xenotransplantation. Again, this is what the document -- the draft guidance document lays out. It also points out biological products, drugs or medical devices sourced from nonliving cells, tissues or organs from nonhuman animals, including but not limited to porcine insulin and porcine heart valves are not considered xenotransplantation products.

Now, we have to, as a result of a lot of consultations with scientists and the various advisory committees and industries and soul searching, we have to ask the industry to take special steps with respect not only to xeno recipients, but their close contacts. And for various reasons, we've abandoned the terms close contacts and have adopted the term intimate contacts. And we include in the document specific examples of what some of these are.

Now, the intimate contacts we described as intimate exchange of body fluids, including

blood or saliva. We say examples include, but are not limited to, sexual partners and people who share razors or toothbrushes with xenotransplantation recipients. Also it includes healthcare workers with repeated percutaneous mucosal or other direct exposures to xenotransplantation product recipients. And we also point out that intimate contacts do not include the simple sharing of housing or just casual contact or just hugging or kissing without the exchange of saliva.

Now, as you certainly know by now, having received many excellent talks certainly yesterday and I'm sure before, because xenotransplantation necessitates the disruption of the recipient's usual protective physical and immunologic barriers, xenotransplantation may facilitate transmission of known or as of yet unrecognized zoonotic agents to humans.

Some xenotransplantation product sources, particularly pigs, as you mentioned yesterday, are being genetically modified in ways that may foster adaptation of zoonoses human receptors.

Basically in xenotransplantation, in inhibiting the immune system and in inhibiting the way for the recipient organism to get rid of the donor graft, you are setting up a wonderful opportunity for agents to adapt and modify themselves, either through recombination of mutation, in a very nice environment, and we're constantly very worried about the appearance of something new, or the modification of something known but not known to cause pathology at the moment or in its present form.

Another issue that needs to be pointed out, and again you've had good descriptions of this, is some xenotransplantation procedures maintain a barrier between host and foreign tissues, such as transplanted cells with a physical barrier around them or ex vivo perfusion with a barrier between the cells and the xeno recipient's blood.

Even when such barriers are nonpermeable for virus the risk of barrier failure require consideration. So the use of barriers does not disqualify someone from being considered a xenotransplantation product recipient.

While we obviously face some major problems, some of which you've already grappled with, the biggest problem we've faced in trying to derive policy for protecting the blood supply is that the risk of zoonotic transmission to xenotransplant recipients and their contacts remain undefined. If we know what we are going to get we can devise a test for it and test units that are donated, but not knowing what may happen, we can't do that. Opposed to that, of course, is the threat of something sneaking through, something like a HTLV1, and possibly not becoming apparent for the next 40 years. We could very easily have a major public outbreak through inattention to appropriate protection.

Balanced against this are the immediate risks. The risks to the public health of blood or blood plasma becoming unavailable are immediate and significant. So one of the problems we typically run into in devising blood safety policy, is that it would be very easy to rule out every possible thing in the world, but it's very possible for small amounts of unwanted blood to get through, you find out about it later, the unit's already been put into thousands of other units into products all over the country. You have to call all of them back in a withdrawal situation, and then you can cause serious shortages of life-saving products. Withdrawal of plasma derivatives to address even small numbers of unsuitable donations can cause serious product shortages. We've seen this

recently with some other policies. They said there are no tests for unknown zoonoses.

And the other big problem we have is that framing questions for -- deferral questions is very difficult. There are two levels of protection in blood donations. The second one -- of course the major one is testing for various known pathogens. The first level of protection is a long list of questions that potential blood donors are asked before they are allowed to even donate blood, and this list of questions is always a problem. The industry hates it. I don't blame them. We don't like it, but it's also necessary. And they are very complicated, very hard to understand. You have to worry about people losing interest and getting confused. And particularly for something like xenotransplantation, it gets very complicated if you have to describe, well, what is a xenotransplant. You heard the definition I gave earlier. If you have to read that off to someone, a layperson giving blood, you can see their eyes glaze over. So we're -- it's very hard to define xenotransplantation recipients, intimate contacts, et cetera, in the context of the blood donor situation.

And there's always a balance between successful yield, in other words, the questions actually catching a potential xeno donor and the confusion that this induces. If it's a question too complicated to understand, the people who should be deferred will answer it incorrectly. And all of these are undesirable situations. It's not a trivial matter to frame questions appropriately.
Just very briefly, to define what we see as the threat to the blood supply in terms of numbers. We figure there are about, maybe about up to 1500 xenotransplantation recipients in the United States. About 500 to 1,000 of these have had autologous transplants of cells grown on a monolayer. Typically -- well, this includes the well-known Epicel products. And there are about 470 other kinds of xenotransplantation product recipients.

Now, we have not approached our policy decisions on our own by any means. We have sought advice from scientists in industry through several meetings of several advisory committees. This just lists the basic history of that. In 1996 there was a draft PHS guideline on infectious disease issues in xenotransplantation, and they recommended deferral of xeno recipients.

December of '97 on the Xenotransplantation Subcommittee of the Biological Response Module Advisory Committee, the deferral of close contacts was recommended. However, Kathy from CBER brought this up at the very end of the meeting and it was answered by the chair without discussion and without a vote. This issue was then, more recently in March of '98, discussed in front of the Blood Products Advisory Committee, that's our advisory committee, they are the advisory committee that keeps track of those of us who keep track of the blood supply.

December of '99 we published the first draft guidance. The first form of what you're seeing now, and we responded to comments made to that.

In January of 2000, again, the xenotransplantation subcommittee discussed the highlights of that draft guidance document and voted on several recommendations. They all wanted us to continue to recommend deferrals of xenotransplantation recipients. They did not like the term close contact and they voted to replace close with intimate, so that they voted to say that the contact of concern for the blood donor setting are intimate contacts. But then we never really defined intimate. And then they voted

in somewhat of a split vote, nine in favor, seven against, to defer intimate contacts of xenotransplantation product recipients.

They were unanimously against deferring healthcare workers who have mucosal or percutaneous exposure to xeno recipients. However we did revisit this issue with the BPAC, as well as some other issues. The regulation with the blood supply is kind of an esoteric effort, and we often find issues that are seen very differently by a Blood Products Advisory Committee and specific -- they are seen elsewhere.

The Xeno Advisory Committee in January of 2000 did allow case-by-case exceptions for deferrals such as exposure to Epicel. I mean, that would be case-by-case deferrals we would sit down as an agency and decide.

Now, they did want to vote -- we have two issues. We have both deferral and withdrawal issues in the industry. Deferral means somebody has deferred from giving blood. They flunked the questionnaire and they are asked not to donate blood. What happens if something slips through that should have been deferred, then you have to get into -- you have to pull it back, and that's called withdrawal. Usually the two are pretty close. They are obviously very closely linked. We usually don't like to have policies which unlink the two.

They did vote then to withdraw whole blood and unpooled blood components from a xeno recipient, that was unanimous.

They voted to withdraw pooled plasma derivatives for donation by a xeno recipient. The reason why it's important to distinguish between pooled and unpooled, it's no big deal to go back and grab a unit of blood and get rid of it if you have found out that afterwards it's been donated. If that unit has already been incorporated into a 10,000 unit pool of plasma and it's made its way into huge numbers of products all across the country, withdrawing everything that that went into could cause serious and immediate health risks, and that's what's going on there when we distinguish between the pooled and unpooled.

And when asked whether we should withdraw plasma derivatives, now pooled plasma for donation by an intimate contact of a xeno recipient, it was a split vote, but they voted against this. It's somewhat of an arbitrary decision, but you have to draw a line somewhere, and they felt the risks, the immediate risk of withdrawing large numbers of products all across the country outweigh the theoretical risk of contamination by donation of a unit from an intimate contact. And notice that this dissociates between a deferral and withdrawal, which is something we generally like to avoid, but in this case it was recommended.

And finally, they supported case-by-case exceptions to withdraw for certain kinds of exposures, ex vivo. This would be typically your -- across a physical barrier or something like that.

Now, they did -- the guidance document that they were discussing at that time did have a list of questions to be added to the questionnaire. They are unanimously against those questions, but they did ask us to go back and reformulate more appropriate questions in further consultation with experts.

And they rejected proposals to rely on xeno educational material in the blood donor setting. What that refers to is when you come in to give blood there is literature that you're handed sitting around while you wait, and you're supposed to read it. It's probably one of the least effective methods of interdicting unwanted stuff from getting into the blood supply. And it was just felt that it would be inappropriate for xenotransplantation because xenotransplantation is so complicated.

Now, one of the members of the Blood Products Advisory Committee, John Boyle, then worked with us directly to formulate a series of questions to make them as simple as possible, as clear as possible, and to fit into the current questionnaire as easily as possible. And what they decided on in summary was to modify -- was to do two things. Basically, to modify a current question to highlight the nature of xenotransplantation as opposed to transplantation of a human organ. And also to introduce one additional new question to grab all of the possible deferrals that we want to catch based on xenotransplantation. And this one question then leads to a set of nested questions if the answer to it is yes. And if it's no you can just keep on going and not get bogged down in all the complicated xenotransplantation issues and understanding them.

And the current question that's modified, what we recommended the new form to be, if in the past 12 months you received blood and organ, skin graft or other tissue transplant from a human donor. If yes, you would defer. Now, what's new about that is from a human donor. And that sets people up for the next question, which is a new question. And that is, have you, any sexual partner, or any member of your household ever had a transplant or other medical procedure that involved being exposed to organs, tissues or living cells from an animals. Now, if the answer to that is no, then you would proceed to the next question and you would not be deferred on the basis of xeno issues. If it's yes you proceed to the nested questions.

The nested questions then lead to the deferrals of xeno recipients, sexual partners of xeno recipients, people who have had repeated exposure to xeno recipients through blood, saliva or other body fluids, through deep kissing, shared toothbrushes, razors, needles, open wounds or sores. The way they are actually phrased is, as I pointed out in this second question down here, if you're flagged by that, in other words, if the answer to that is yes, then the next question would be, was it you, a sexual partner or some other member of your household who had a transplant or otherwise was exposed to organs, tissues or cells from an animal. And then it instructs you to -- instructs the test, person monitoring the test to defer if the answer is you or sexual partner. If it's another member of the household you are directed to go to the next question, which is have you been repeatedly exposed to blood, saliva or other body fluids from these individuals through deep kissing, shared toothbrushes, razors, needles, open wounds or sores. If the answer is yes, then you defer.

And then, finally, one point to remind you of in the guidance document, the FDA will consider on a case-by-case basis, deferral for certain ex vivo exposures to a well characterized cell line or exposure across a physical barrier.

We are trying to leave ourselves open for changes in the field and also for complexities. The bottom line is that it's a very complicated endeavor to try and ask these complicated questions in a blood donor setting. We've come up with a series of questions which capture most of what we want to capture but not everything perfectly, and it's generally felt to go beyond what we're recommending is going to cause more confusion and more

trouble than the benefit it would confer upon it. Thank you, very much. Do we have a question period or just --

DR. VANDERPOOL: Why don't you take a seat at the table, Dr. Dayton, and that way, as soon as our two other people with public comments, then we'll all join together in discussions of questions and so on.
We can ask at this point if you have any questions of clarification from what Dr. Dayton just reported?
James.

DR. WRIGHT: Yeah, I have one clarification. The way that was worded, organs, tissues or living cells, that would seem to include porcine heart valves. I mean, would it not be organs, living tissues or living cells?

DR. DAYTON: We specifically exclude porcine heart valves because they are fixed in glutaraldehyde fixatives and they are not living. We actually specified them as specific in the document. And that's a good example, as well as being a specific exclusion.

DR. WRIGHT: If it were just organs, tissues or living cells, then that would include the porcine heart valves. But if it's specifically stated elsewhere --

DR. DAYTON: The heart valves are not living.

DR. WRIGHT: No, but the phrasing is organs, tissues or living cells. I mean, to be more precise, it would be organs, living tissues or --

DR. DAYTON: Yeah. I think that's clear when you actually read the document.

DR. WRIGHT: Okay.

DR. VANDERPOOL: Dr. Wright, is your suggestion to modify it to be living organs, tissues or cells?

DR. WRIGHT: Well, you wouldn't transplant a nonliving organ, but you could transplant a nonliving tissue like the heart valves.

DR. VANDERPOOL: Okay. Other questions for clarifications? Let's have the two persons for comment, public comment, and then open it for committee discussion.

DR. GROESCH: Our first commenter is Ms. Kay Gregory, she is the director of Regulatory Affairs for the American Association of Blood Banks, and she's making a joint statement on behalf of the American Association of Blood Banks, America's Blood Centers and the American Red Cross.

MS. GREGORY: Thank you. Let me begin by just briefly explaining who we are. The American Association of Blood Banks is a professional association for both individuals and institutions, and we represent all aspects of the blood community, both the collection side and the transfusion medicine side.

America's Blood Centers is an organization that represents community-based blood centers, and they collect approximately half of the nation's blood supply.

And the American Red Cross, of course, collects the other half of the blood supply. So the point I'm trying to make is that this statement is on behalf of the entire blood community, both on the collection side and transfusion sides.

Recognizing the potential of transmitting zoonotic pathogens to patients by xenotransplantation, the AABB, ABC and ARC agree that xenotransplant recipients are unacceptable donors of allogeneic blood and tissue. Under current donor restrictions regarding health medication use, virtually no xenotransplant recipient would be a qualified blood donor at this time. In other words, they'd be ruled out for all kinds of other reasons.

The theoretical risk from zoonoses was well articulated in the August 1996 draft Public Health Service Guideline on infectious disease issues in xenotransplantation, which included language appropriately recognizing the primary responsibility of the transplant community for apprisal of their patients about zoonotic risks. As its January 13, 2000 meeting, the Xenotransplant Subcommittee of the Biological Response Modifiers Advisory Committee endorsed our position that primary responsibility for notification and education of xenotransplant recipients about refraining from blood and tissue donation lies with the institution performing the clinical trial.

We strongly support implementation of this aspect of the Food and Drug Administration's most recent draft guidance. Blood collection facilities can reinforce the prohibition on donation by including the xenotransplant exclusion in the written materials blood donors are required to study before each donation. This avoids addition of time-consuming, confusing and unvalidated questions that FDA suggests adding to the donor interview in this guidance. And I might add parenthetically that we are working on a uniform educational material to be used for all blood donors that is much simpler than the one that is in use now, and I think may answer some of the concerns that nobody reads in this, nobody pays any attention to it. We really are working very hard to make sure that is not the case.

Donor screening is already lengthy and complex. The AABB uniform donor history questionnaire, which is approved by the FDA, contains 32 separate elements, including inquiries into highly sensitive personal area of sexual activity and drug use and references to such rare diseases as Babesiosis and transmissible spongiform encephalopathies. FDA proposes to add additional complex questions to this process. REDS investigators have reported that 1.8 percent of the anonymously surveyed accepted blood donors admit to deferrable risks, and we suspect that a substantial proportion of that percentage is due to the length and complexity of the donor interview.

An AABB-sponsored interorganizational task force on streamlining the donor history questionnaire has recently conducted focus group evaluation of the xenotransplantation questions proposed by FDA in their current iteration. They provoked multiple recommendations for editing and shortening the questions, splitting questions into their component parts and more precise definition of such terms as repeatedly and keep kissing.

Increasing the complexity of the donor screening process for marginal theoretical risks will detract from its efficacy for documented risks like traditional viral transfusion

associated infections and malaria. The result may be a paradoxical decrement in transfusion safety, in addition to any unintended donor loss.

We maintain that proposed donor questions in this draft guidance remain too arcane to add to the current screening process and may produce donor confusion. This would result in unneeded deferrals at a time of borderline blood supply adequacy. At a minimum, additional questions proposed by the FDA for the reduction of hypothetical risk must be validated for comprehension before being added to what is already referred as the donor interrogation process.

The requirement for deferral of sexual, household and other close contact is unsupported by any evidence of transmission of potential or unrecognized pathogens to such non-immunosuppressed contacts after exposure to xenotransplantation recipients. We understand that the transplantation recipient will be immunosuppressed and be at theoretically increased risk for zoonoses. We do not accept that the non-immunosuppressed contacts are at an increased risk and object to their inclusion. In the prior draft, deferral of healthcare workers, laboratory personnel and other individuals who have had contact with blood and body fluids from a xenotransplantation product recipient, was subject to the same criticism, and this language has been dropped from the most recent draft. Furthermore, it's a slippery slope from such donor deferral to disqualifications of larger populations with significant occupational animal exposures, such as abattoir workers, farmers, veterinarians and medical researchers.

The AABB, ABC and ARC, suggest that a risk assessment be undertaken among non-xenotransplant individuals with close contact to the relevant animal species for evidence of disease associations that would support concerns of zoonotic transmission of disease causing organisms by donor blood. Given the small numbers of the xenotransplants currently being performed and the potentially large populations with contact to nonhuman primates and swine, these epidemiological studies can be carried out before xenotransplantation becomes prevalent, constituting a zoonotic threat to significant numbers of patients and their contacts.

In summary, the AABB, ABC and ARC would like to stress the following points: We accept the necessity to defer recipients of xenotransplants, and respectfully suggest that the transplant programs have primary responsibility to initiate this process as part of informed consent. Blood collection facilities will be happy to reinforce this action with written predonation information.

The addition of unvalidated donor interrogation questions for the theoretical risk of xenotransplantation or any theoretical transmissible entity, may, at worst, paradoxically increase other risks of transfusion, and at best will contract an already shrinking donor base. At a minimum, such proposed questions must be validated for a minimum level of sensitivity, specificity and predictive value, as would any in vitro diagnostic assay required by the FDA.

Deferral for contact with xenotransplant recipients is unwarranted at present, and the risk of such contact is amenable to study in populations with occupational exposure to the relevant species. Thank you.

DR. GROESCH: Thank you. Our next commenter is Dr. Celso Bianco, he's

Executive Vice-president of America's Blood Centers.

DR. BIANCO: Thank you very much for the opportunity to comment. I'm not going to speak or read a statement. I'm a physician in transfusion medicine. I want to just reemphasize what Kay just said to you. I hope that if you hear it twice it will resound better.

I just want to emphasize we collect from volunteer donors about 14 million units of blood every year. There are about 4 million recipients of those transfusions. The sense that I have is that since we know there are about 1500 recipients of xenotransplants today, the feeling I have is that we are throwing a needle in a haystack, and we go to look for it a few years later when potentially those individuals could transmit it to somebody else.

If you also calculate that even if those questions had add 30 seconds or a minute to the miracle history process, this will add 14 million minutes or 7 million minutes, or about 14,500 days of interrogation to our donors. We have to ask the value. We already have issues with medical history that we are very concerned about. The donors, we ask them about sexual behavior, have you ever -- have you had sex with another man since 1977, which are not the correct questions, because the actual risk on the window period that we have today that we use molecular screening for HIV, as you must have heard, that about a week ago or so a text was licensed, is that in that window period of about ten days since the infection until the virus can be detected. So we hope that you can help us to focus the issue and to have us, instead of asking the questions as a recommendation, to have us simply add informational material and emphasize with the transplanters, they are critical, they have long follow-up of the recipient, that's what you are recommending, those are the people that have to educate them to stay away from blood donation. Thank you.

DR. VANDERPOOL: We have only a few minutes to, 30 minutes to talk about these issues that in ethical terms present a classic dilemma between the duties of not harming and preventing harm over against the duties to benefit others as much as possible. This of course as we already see, the lines have been drawn and it can be an emotional issue, and insofar as we can give wisdom, let's do so. If we can reach a consensus, by all means, let's try or let's do that. But I think let's just open it up for comments from all, each and all members of the SACX committee or nonvoting members from Federal agencies. Mike, let's start with you.

DR. SWINDLE: I'd like a clarification on something you said when you were speaking. You said that the existing form results in 1.8 percent rejection of donors; is that correct?

DR. BIANCO: I think it was in Kay's statement. There is a large study of blood donors that has been carried out for about ten years, it's called REDS, retroviral epidemiology donor studies, supported by the National Institute of Health and Blood Institute. There was a survey of about 30,000 individuals that had donated. The survey was done anonymously. And the questions that are asked of donors were repeated essentially in this survey in different formats, different shapes.
There were, I don't recall exactly the numbers of returns, but it was a reasonably high rate of return, 60 percent or so, I believe. And among those that returned the answers, what we recognized were the people that did the study recognized that 1.8 percent had

revealed or revealed a risk that if they had revealed that risk at the time of donation they would have been deferred as blood donors, their donation would not have been accepted. So there are issues of comprehension with the current questionnaire. That was the conclusion of the study.

DR. SWINDLE: Can I get you to clarify that a little further? Because I definitely misunderstood what you said. What I thought the statement said was about two percent of all people who walk in for donations get rejected because of your questionnaire, but that's not the case?

DR. BIANCO: No.

DR. SWINDLE: I do have a follow-up to this, because you actually have a broader issue in effect now, and that's this travel to Europe thing, which is certainly costing you more donors than xeno ever would on that. And I'm curious about what percentage loss you had in this last six-month period of time?

DR. BIANCO: Well, I just want to finish on the first one. Normally -- normally. Usually the average -- in the average donor population, about 15 percent of the donors are rejected in medical history. About five percent of those are rejected because of low hemoglobin or because of some physical, hypertension or something physical something like that. The other eight to ten percent are rejected because of medical questions.

What is expected in terms of the implementation of the CJD referrals? By October 31 we start the first stage, May 31st at the end, October 31st, we expect from that same REDS study and some calculations that were made, we'll lose about five percent of our current donor base. The loss will be much higher, obviously, in cities like New York or Washington or LA where people travel more, and less in more rural areas of the Midwest, but that's what the survey has indicated to us.

DR. VANDERPOOL: Ms. Gregory.

MS. GREGORY: Also, I wanted to add that it's very difficult to estimate what our loss of donors will be for various CJD deferrals, because we have no way of measuring. It gets such wide publicity, that a number of people never appear to donate again that are lost to us, we have no way of tracking that. We can track those who come in and answer the question and we defer them. But a number of blood centers, for example, sent out letters and said if you meet this criteria, please don't come in and waste your time because we won't be able to accept you. So it's very difficult to know what the loss actually is.

DR. VANDERPOOL: Okay. A comment. Dan Rotrosen, our representative on SACX from the NIH is not with us today, but in his stead Dr. Shiv Prasad presides. Okay. You are filling in as our rep from the NIH and you have some comments on the FDA guidance document.

DR. PRASAD: Yes. Thank you, Dr. Vanderpool. I'd like to summarize for the committee the official NIH comments in response to the FDA draft guidance. In general, the NIH concurs with the FDA guidance. When one weighs the potential risk of zoonoses transmission against the small benefit that the small number of potential

donors of blood and blood products, it is certainly an acceptable precaution to defer these xenotransplant recipients from donation. It's also a wise precaution to defer the intimate contacts from donation. However, the NIH comments are that this can be periodically reviewed as more data become available on the risks of zoonoses transmission. The NIH recommends that there should be further consideration of healthcare workers as intimate contacts.

And finally, the donor screening questionnaire should be tested and validated before it's implemented to ensure first that it's comprehensible to the general public and, second, that it can identify and screen out potential xenotransplantation recipients. Thank you.

DR. VANDERPOOL: Thank you. Is there, Dr. Dayton, some particular plan in place for validating the wording of this before it goes into effect?

DR. DAYTON: No, not at the present case. We often get this request and we often don't have the resources to validate every request like we'd like to. I believe the question will be validated on its own as it's used in practice and this typically happens.

DR. VANDERPOOL: Marian.

DR. MICHAELS: I have two questions for points of clarification. The one had to do with the recommendation from the Food and Drug Administration. Was I correct in that it said in the last 12 months have you received a organ, tissue or cells?

DR. DAYTON: That was from humans and that's a preexisting question.

DR. MICHAELS: Thank you. And then the question that I had for the comments from the blood bank community, your objection is mainly to it being -- the intimate contacts be included, but you would be okay -- another statement that I might have misunderstood, that you also felt that the transplanter should be the one telling the transplant recipients, and that you didn't want that as a question as well, or you were willing to have that as a question. I have concerns that from the public health standpoint in protecting the blood supply I would not rely just on the transplanters, though I feel that they would have the best intention.

MS. GREGORY: We would prefer not to add any questions to the questionnaire. It's already long, complicated and we have difficulty with it. On the other hand, we are quite willing to add information to what we call our educational materials and to make sure that all of our staff are aware and, you know, discuss it with a donor, but we just don't want to have to add a question.

DR. VANDERPOOL: And you're saying you wouldn't want to add a question that would exclude recipients also?

MS. GREGORY: Right. We would prefer -- we don't want to add any questions. We agree that recipients need to be excluded, we certainly agree with that, but we just would like to not to have to add any more questions that apply to very few individuals but need to be asked to huge numbers of individuals.

DR. VANDERPOOL: Of course one of the problems here is that on the consent forms that, the only form I've seen, and on the working group's consent recommendation, we

would certainly add no blood donations, but whether that would be sufficient to protect the blood supply is a question for certainly the experts on the committee to deal with. Do you have a comment to that, and then let --

MS. GREGORY: Let me add one more thing. And that is because of all the other things that we're already asking donors, anyone who is a xenotransplant recipient would be very unlikely to qualify as a blood donor anyway. So we think we would be screening them out without having to ask a specific question.

DR. DAYTON: We are certainly sensitive to industry's objections and we are very well aware of them. If you want to pick up the intimate contacts, then you have to ask questions, because you can't do that by informed consent. So the strong recommendation that we defer intimate contacts necessitates asking questions about intimate contacts. If you ask questions about intimate contacts, you really have to ask questions about being a direct recipient as well. In fact, asking a question about being a direct recipient leads in, conceptually, to the close contact questions.

DR. BIANCO: If I could just add, and particularly to what Dr. Dayton just said, I respectfully disagree with that. I think what I hear from you and this committee and this discussions on consent, this is an educational process, not just for the recipient, but for the entire family. If there is -- and all the people that live with that person that received a xenotransplant. They are the ones that would be really at risk and not so -- this is much more than the so distant blood recipient.

That's why I would ask that, from the public health point of view, that you focus on an educational program now of these 1500, 2000 people and later, as I hear other activities that you have in terms of more promotions. Every message that is sent about xenotransplant from the Public Health Service or from other official organization should contain a message that these people should not donate blood. That would do much more than simply adding to the process of donation and trying to fish these rare events that will certainly, in the middle of everything, question about babesia, shark diseases, hepatitis, sexual behavior, and all that, 32 questions that we have, will be missed.

DR. VANDERPOOL: We have a number of people who are acquainted with hospital infectious disease issues and community involvement, so please join in this discussion. Obviously it's a critical set of questions. First Dr. Chapman, then anyone else, please join in.

DR. CHAPMAN: I just wanted to get a point of clarification. Andy, you said the strong recommendation to defer contacts of xeno recipients requires questions, but I'm confused on whose strong recommendation that is. Are you still referring to the acclamation by the chair of the xeno subcommittee or did the --

DR. DAYTON: No, in many subsequent meetings we had that mandate.

DR. CHAPMAN: From the Blood Products Advisory Committee?

DR. DAYTON: Yes.

DR. CHAPMAN: Because I don't recall that from the meeting I attended.

DR. DAYTON: I can pull out the votes again, but that was understood from the Blood Products Advisory Committee that they actually wanted the intimate contacts, what I don't remember is if it was a unanimous or split vote.

DR. CHAPMAN: It wasn't unanimous, I was there.

DR. VANDERPOOL: Bill.

DR. SCHECKLER: I think there's two issues involved here. One is from the xeno point of view it seems to me the most feared viruses are the retroviruses, HIV, HTLB1, would be the examples of those. And conferring with my expert to the right here, and based on my own knowledge, that's the model that you could decide the issue between sexual contacts and intimate contacts in the household. You have, for example, the model of kids with hemophilia that developed HIV and it does not appear that the siblings or the parents of those kids are at risk for acquiring HIV. And it would seem to me that, at least in terms of retrovirus transmission, this sort of second category, other than sexual contact of frequent, you know, sores and so forth and so on, is so complex as to be difficult to deal with. So that seems to me might be eliminated.

It seems to me that xeno recipients themselves are sort of automatically eliminated based on all of those questions. I mean, I can't donate blood anymore because I'm on medications for my heart. I think all of the questions that are already in existence, and they are in the book here under Tab 7, would virtually eliminate all of the other xeno recipients. So then you're left with, in my estimation, the sexual contacts, and I don't know how to rephrase that under the existing questions that are already there.

But the second piece of this, it makes a certain amount of sense to me, is the needle in the haystack analogy. The tiny number of people that have received xenotransplantation to date, which other than Epicel, is about less than five hundred, and their sexual contact, sexual partners is a minuscule number compared to the millions of people that donate blood. So asking this question, the risk benefit may very well not be there at all, and maybe the educational program is the thing you start with until such time as xeno reaches some sort of reasonable threshold at which statistical probability might lead you to think these people might be donating blood despite the fact that informed consent, which includes family members right now as I understand it, is insufficient. So I'm sensitive to the blood donor community based on the science of this.

In terms of health workers that are exposed to xeno members, frequent or recurrent needle stick or other kinds of exposure to folks that receive xenotransplantation would be an extremely rare event, unless you had a truly incompetent health worker. A single event is something else, but, again, that risk even with HIV is even very small.

DR. VANDERPOOL: While it's rare, of course it could be a proximated catastrophic event should an untoward event occur. Jon Allan and others on the committee have comments about this? It's a tough question.

DR. ALLAN: Yeah. I was on the xeno committee, the Efficacy Xeno Committee. It was a little clearer, because when we discussed it it was based on the fact, you know, xeno's going to happen and you are going to be transmitting organs and you are going to

be transmitting all these things, then you really want to have this in place because this is a real risk. I mean, there's a real theoretical risk, let's put it that way. Based on AIDS and HIV, I mean, you don't want to -- it may be a small theoretical risk, but if one infected recipient's bloods gets into the blood supply, you may have thousands and thousands of people getting infected, and that's the big problem. It's that exponential transmission rate, and that's what you have to worry about. At the same time, I'm also hearing, it's like how many xeno recipients are there actually going to be, ever, you know, whether there's a good promise for xeno or not.

So that's the crux to me, is do you implement this thing and let's say that only 100 xeno recipients are ever going to get any products so --

DR. DAYTON: These are not etched in granite. I mean, if it turns out that xeno is abandoned, of course the policy can be reversed, it's not terribly hard to do.

DR. ALLAN: But you've already got some patients in the pipeline that have already received products, so what's your read on when to implement this?

DR. DAYTON: Well, we haven't analyzed it along those lines yet. Our basically policy decisions were predicated on assuming it would be an expanding area of endeavor. If that drastically changes we'd have to rethink it. But we did follow exactly the line of thought that you just said, and really echoes -- if there's something bad and it's going to get out, this is where it's going to get out.

DR. VANDERPOOL: Louisa.

DR. CHAPMAN: I just want to make a point of clarification for the public record, because it may matter at some point. There was the initial xeno subcommittee discussion of this in which the deferral of contacts was done by acclamation of the chair without discussion. According to your slides at the subsequent xeno subcommittee, discussion in response to the question should you defer intimate contacts of xenotransplant product recipients, there were nine yes votes and seven no votes, so I would not describe that as a strong, that was a split vote. There was a subsequent discussion at the BPAC committee and I think that was also a divided vote, so --

DR. VANDERPOOL: I remember being on the xeno committee also -- this is a filler since nobody else is saying anything -- and we went round and round on this issue, debated back and forth, and it's a solid made judgment, because the risks are only theoretical, and with this extra wording there appears to be an adverse affect on the number of donors. Form is long already. I even remember thinking, well, why don't they bump off some of the other things on that form and put this one on, because this is, this is a critical issue.

One of my concerns, and this is something we voiced in our working group on informed consent when we had our breakout sessions, is there's either a need to go to the community and get some sort of consent, which would be extremely hard to do, some people are pressing for this, extremely difficult. I mean, who's the community, who represents the community. There's no such a thing as a community consent, it would be assent or permission or something like that. Or, we take every precaution possible to protect the public so the public doesn't lose faith in its protective agencies, and that way you have a reason not to go through the arduous process of public assent through

elected representatives and so on.

So one side of me is thinking that -- and we ought to err on the side of public protection at this point. And if we see that the information is that we shouldn't go that direction, then let's pull back. But, obviously, the agencies that are most concerned about public protection are the ones who are pressing for this, for this guidance, and those who are concerned about not shrinking the already limited blood supply are pressing on the other side. Analysis, but no answers. Marian.

DR. MICHAELS: I just had a point of clarification just because Jonathan Allan brought up some numbers and I wanted to find out how accurate those numbers may be. So we're talking about a potential risk to the recipient, those people should be deferred. A potential risk if it gets into the recipient getting into the intimate contact. If an intimate contact had donated blood, how many people does that blood product go to?

DR. BIANCO: A blood product will, in general, for fresh full blood component will go at most to three or four recipients, sometimes the unit is divided for small recipients. In the case of plasma derivatives, a lot of the plasma is then pooled into plasma derivatives for manufacture. Immunoglobin and albumen and all that, then those are very large pools of 50 or a 100,000 units. So that's why the question of the withdrawals.

I was just hearing this discussion and it gave me -- what is the difference in terms of transmission between a contact and a recipient of blood? And the potential that they are going to be the source of that exponential spread of the virus?

I think that because of the sensitivity of blood issues and because of the AIDS crises, the tragedy that we saw in the early '80s, we are all very concerned. But here, the real focus is the contact to that recipient, much more than the rare event. Only five percent of the normal population donates blood and they donate it once or one and a half times a year. So that's a rare event in the thing, while these contacts are always there with a hundred percent or less if they are celibates of the recipients of general transplants.

DR. VANDERPOOL: Is there any concrete evidence about the number of persons who would otherwise give blood with this kind of additional addenda, these addenda to the form, who would just say, hey, you know, up to this point I'm okay, but I'm walking out of here because this is too much. Do we have any information about those who would end up not staying and giving blood because these questions would be on the form?

DR. BIANCO: No. This is not -- we don't have that data in this format. The data that we have is that about only 30 to 40 percent of the first-time donors come back, and also we have a gradual erosion of the donor base because the donor gets hurt. The low frequency of donation also, that when we encourage people to donate every eight weeks, is 1.5 percent around the country, and it's harder to get up. And we do a lot of first surveys and focus groups and all that identify that one of the major obstacles is the medical history, that it's long, it's boring, intrusive and even for the repeat donor the same questions are asked every time, just plain boring, and they don't bother.

DR. VANDERPOOL: Does it make sense at this point -- excuse me. Karren.

MS. KING: I have a question for Ms. Gregory. Just to clarify, you had said earlier you posted in your questions even for someone who may have been a recipient, that hopefully education would be provided by the center, but also that materials would be at the blood centers. But then you also later said that they would be educated possibly by someone on your staff about the materials. Is it both?

MS. GREGORY: I may have been misleading. We have material that we give to every donor and that we require them to read before they donate. And then if they have any questions our staff are able to spend more time with them and answer more definitively. So that's what I really meant was, it needs to be two-pronged. We need to have something in our educational material and we need to make sure that our staff is well versed so that when someone does have a question they are able to explain it adequately.

MS. KING: I guess the only thing I would add is I would have concern, if we do think it's important these individuals not donate, to leave it to them to read something that they may or may not read, as we all know when we are given information. I would be concerned that we would be relying just on that to have them screen themselves out. If they happen to show up and not even receive education elsewhere.

MS. GREGORY: I think that's a common conception, but I don't know that we can be any more certain that they would understand the question we're asking them and answer the question appropriately if it's a very long and convoluted, difficult to understand question.

MS. KING: I agree. It depends on the wording of the question.

DR. VANDERPOOL: Dr. Swindle.

DR. SWINDLE: Yeah. You call me every 60 days regardless. I've been giving blood for 25 years this way, and I don't read the information that you give me and I check all the questions off after this period of time without even reading them. The questionnaire doesn't stop me from coming back or anything like that. I'm just not -- maybe I'm unusual, but the question -- the length of the questionnaire and the material for the chronic donor, I don't think would be an issue.

I find the questionnaire silly, and I think it should be totally rewritten from scratch and you should eliminate true foolishness, which does exist on the questionnaire, I think that may help things. But in my mind the length of the questionnaire, the educational material for repeat donor is not an issue.

MS. GREGORY: Let me say that we would agree with you. As a matter of fact, there is an interorganizational task force that has been working for over two years to do just that. To look at the questionnaire, simplify it, make it shorter if we can, or at least make it easier to understand, make the educational materials a lot more easier to read and take out all the garbage that doesn't need to be there. And I should perhaps say take out everything that FDA will let us take out, because there are some things we probably would like to take out that at the moment they have told us we cannot take out.

DR. VANDERPOOL: Does it make sense to the committee for us to at least take a sense of the meeting poll? Or is this just too tentative for us to even do that? Does it

make sense for us to say -- to do a sense of the meeting for this discussion? Everyone is obviously not here so we need to get a count of SACX committee members who are still present. Since the meeting being whether we would in general support the FDA guidance statement in principal, support the FDA guidance over against -- in principal. We would prefer that we would adopt -- our sense would be to adopt the position of the blood bank groups. Does it make sense to first do a census meeting vote or not?

DR. BLOOM: I'd like to know --

DR. VANDERPOOL: Do we have to think about this a lot more before we do that?

DR. BLOOM: I was just going to say I'd like to know if everyone here feels that you've discussed it enough thoroughly to take a meaningful vote.

DR. CHAPMAN: I was going to say the same thing. The committee members might want the opportunity to review the transcripts of the previous advisory committee meetings somewhat before committing a recommendation to the Secretary, which is sort of what a vote of this committee --

DR. VANDERPOOL: Would this go into effect before our next meeting in July or not?

DR. DAYTON: You mean the draft guidance?

DR. VANDERPOOL: Yes.

DR. DAYTON: It's out there as draft, which just means it's for comment. Draft guidance tends to become a de facto standard, but when we get comments to this then we incorporate those comments and come back with a final guidance, which, of course, there's no such thing as a final guidance. So technically it's out there for comment.

MS. GREGORY: And it's out there for comment. The comment period doesn't close until May the 13th.

DR. VANDERPOOL: The comment closes May 13th and we have our next meeting probably in July. Okay. All those --

DR. KASLOW: Just a quick question to Louisa or the FDA folks. Do the transcripts contain or is there a place where we could go to find what little epidemiologic information might have been gathered or offered in testimony or comments to the committee, the other committees, is it worth our even looking?

DR. BLOOM: I don't think there's any epidemiologic evidence to be gained. You're welcome to look at the transcripts, they are on the Internet. It might be good for sleeping.

DR. VANDERPOOL: Okay. The first vote would be all those in favor of taking a sense of the meeting vote let it be known by raising your hand. Okay. Discussion prevails, the sense of the meeting fails.

I do think we have -- this is a very significant issue that does involve our sense of what

risks are out there over against our great concern to have a sufficient knowledge base before we feel that we can take a vote. One of the reasons why I held up my hand is because I was involved in hours of previous discussion over these issues.

We're really at the end of our day and it's been a, I would say a great time together, a very important meeting. We have accomplished a great deal.

I continue to be concerned about how much of what we do and what we say will reach the public. I think we all feel that we want to be -- we feel deeply publically accountable and hope that some of our deliberations will make it into the media and that the public will know that they are a group of people who are seeking as very best we can to find reasonable judgments and to do as much as we can to bring insight to bear on issues relating to xenotransplantation.

One of our challenges, since we are not going to be able to talk about, is what will our next topic of our next meeting be. Please -- Mary's commission is to write to us and ask for our suggestions regarding those topics. Let's please all do reply to her.

I think what we've seen over the last two days is that our workload is significantly heavy and certainly going up rather than easy. That's, in my judgment, as it should be, because now we've been at this for a year and there are -- as we continue to demonstrate to ourselves, there are a lot of very important issues. And I think we're increasingly up to the statue of being able to wrestle with the data, and on occasion, as we just saw, say we're not ready to take a position but on occasion take position.

I urge us all to make our contributions despite of our busy schedules to the two working groups so we can move on to the exciting possibility that other working papers will need to follow.

But God speed to all of you and thank you, all of you who have publicly attended to these meetings, for your patience, for your assistance. And God speed to all of you in returning to your respective destinations. Thank you.

(Meeting adjourned at 2:03 p.m.)